Comments by MRA Section

Initiative: Microbial Risk Assessment Guidelines - Peer Review Comments and Workgroup Responses
Report Date: 2/2/2012

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
0.	Darrell W. Donahue, PhD	-	45	**Excerpt Text:** 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.	No response needed
0.	Darrell W. Donahue, PhD	10A	128	**Excerpt Text:** 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.	No response needed
0.	Darrell W. Donahue, PhD	10B	129	**Excerpt Text:** 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.	Edits were made to chapters 4 and 5. One new graphic was added.
0.	Darrell W. Donahue, PhD	10C	130	**Excerpt Text:** 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.	Edits were made in chapter 1 to better introduce the guideline.

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0.	Darrell W. Donahue, PhD	10D	131	**Excerpt Text:** 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.	Although other stakeholders may find the document useful, expanding the specific audience of this document beyond risk assessors is not within the scope of the document.
0.	Joseph N.S. Eisenberg, PhD	1A	132	**Excerpt Text:** 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.	Chapter 6 was not intended to be lumped in with chapters 7 and 8. In the current format the chapters can be read alone.
0.	Joseph N.S. Eisenberg, PhD	10A	180	**Excerpt Text:** This is an excellent document to have as a resource for risk assessors.	No response needed
0.	Joseph N.S. Eisenberg, PhD	10B	181	**Excerpt Text:** 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.	The workgroup wanted to maintain clear presentation of material from different sources. Editing material from other sources to synthesize was deemed unnecessary. However, some of the longer content from other sources was shortened and moved to text boxes for clearer presentation.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
0.	Joseph N.S. Eisenberg, PhD	10C	182	**Excerpt Text:** 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.	Section 1.10 on uncertainty and variability has been added.
0.	Joseph N.S. Eisenberg, PhD	10D	183	**Excerpt Text:** While focusing on risk assessors this document is applicable to stakeholders as well.	No response needed
0.	Jeffrey K. Griffiths, MD, MPH	10A	246	**Excerpt Text:** 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.	More electronic citations have been added. Repackaging those resources for distribution is beyond the scope of this project.
0.	Jeffrey K. Griffiths, MD, MPH	10B	247	**Excerpt Text:** In general the document is clear and the flow within chapters is logical. I have noted places where this could be improved.	Edits to improve flow have been made.
0.	Jeffrey K. Griffiths, MD, MPH	10C	248	**Excerpt Text:** 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.	Jargon is explained where needed, but is necessary to maintain in the document because jargon is something risk assessors will need to know. Where practical an additional illustration was added.

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0.	Jeffrey K. Griffiths, MD, MPH	10D	249	**Excerpt Text:** 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.	Expanding the document to audiences beyond risk assessors is beyond the scope of the document.
0.	Mark W. LeChevallier, PhD	10A	287	**Excerpt Text:** 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.	No response needed
0.	Mark W. LeChevallier, PhD	10B	288	**Excerpt Text:** Besides the comments above where better linkages and be made within the chapters, over all the Guideline has a good flow and continuity.	No response needed
0.	Mark W. LeChevallier, PhD	10C	289	**Excerpt Text:** 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.	No response needed

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
0.	Patricia L. Meinhardt, MD, MPH	10D	319	**Excerpt Text:** 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.	No response needed
0.	Patricia L. Meinhardt, MD, MPH	10D	320	**Excerpt Text:** 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.	No response needed
0.	Patricia L. Meinhardt, MD, MPH	10D	321	**Excerpt Text:** 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.	No response needed

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0.	Christine L. Moe, PhD	10A	384	**Excerpt Text:** 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. **Image 384 shown below**	Where practical an additional illustration was added. Examples and case studies were not added for two reasons. First, the workgroup found during development of the document that selection of case studies was very difficult and second, at this stage in development of the document, any new examples would not have been peer reviewed.
0.	Christine L. Moe, PhD	10A	385	**Excerpt Text:** 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.	These resources were added.

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0.	Christine L. Moe, PhD	10B	386	**Excerpt Text:** 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.	Summaries for each chapter were added.
0.	Christine L. Moe, PhD	10C	387	**Excerpt Text:** 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".	The document has undergone another round of technical edit.
0.	Christine L. Moe, PhD	10D	388	**Excerpt Text:** 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.	This document was not intended for a stakeholder audience.
0.	Gary S. Sayler, PhD	10A	419	**overall utility of guideline** **Excerpt Text:** Very good, 8 on a scale of 10. Clarity in modeling and uncertainty analysis could be improved	Edits have been made to the modeling and uncertainty sections.
0.	Gary S. Sayler, PhD	10B	420	**Flow and continuity** **Excerpt Text:** 7 on a scale of 10. Basic organization framework very good. Chapters 1-5 could be improved too many points of view.	The workgroup wanted to present different points of view, so risk assessors would have options to consider. As a guideline this presents various options for risk assessors to consider.

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0.	Gary S. Sayler, PhD	10C	421	**Consistency of document in language and level of detail** **Excerpt Text:** 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.	The workgroup decided different points of view were important to capture. The document is not necessarily meant to be read front to back, so redundancy is built in to the question and answer format.
0.	Gary S. Sayler, PhD	10D	422	**Applicability to stakeholders and risk assessors** **Excerpt Text:** Excellent, 9 on a 10 scale.	No response needed.
0.	Donald W. Schaffner, PhD	10D	448	**Excerpt Text:** 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.	Edits have been made, but the workgroup decided to maintain the level of detail.
0.	Donald W. Schaffner, PhD	10D	449	**Excerpt Text:** 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.	This document was not specifically geared to a stakeholder audience. The workgroup believes this document will be useful for government risk assessors.
0.5.	Tony Cox, Jr., PhD	1A	1	**Excerpt Text:** 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.)	No response needed.

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0.5.	Tony Cox, Jr., PhD	1A	2	**Excerpt Text:** 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.)	The workgroup recognizes that this is a burgeoning field. The attribution modeling in section 5.2.4 was enhanced and a discussion on fate and transport was added (section 5.0).
0.5.	Tony Cox, Jr., PhD	1B	3	**Excerpt Text:** 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.)	A technical edit was performed.
0.5.	Tony Cox, Jr., PhD	1C	4	**Excerpt Text:** Yes, the Q&A format is suitable for multiple purposes.	No response is needed.

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0.5.	Tony Cox, Jr., PhD	1D	5	**Excerpt Text:** 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?"	The workgroup recognizes that this is a burgeoning field. The attribution modeling in section 5.2.4 was enhanced and a discussion on fate and transport was added (Section 5.0).
0.5.	Darrell W. Donahue, PhD	1A	46	**Excerpt Text:** 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.	No response needed.
0.5.	Darrell W. Donahue, PhD	1B	47	**Excerpt Text:** 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.	Numbering has been added to appendix A.
0.5.	Joseph N.S. Eisenberg, PhD	1B	133	**Excerpt Text:** 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.	No response needed.
0.5.	Joseph N.S. Eisenberg, PhD	1C	134	**Excerpt Text:** 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.	Expansion beyond food and water is beyond the scope of the document.
0.5.	Joseph N.S. Eisenberg, PhD	1D	135	**Excerpt Text:** 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.	Expansion beyond food and water is beyond the scope of the document.

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0.5.	Jeffrey K. Griffiths, MD, MPH	1A	184	**Excerpt Text:** 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.	No response needed.
0.5.	Jeffrey K. Griffiths, MD, MPH	1B	186	**Excerpt Text:** 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.	The format of the abbreviations was not changed.
0.5.	Jeffrey K. Griffiths, MD, MPH	1C	190	**Excerpt Text:** 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.	Jargon is defined where the workgroup felt it was necessary.
0.5.	Mark W. LeChevallier, PhD	1A	250	**Excerpt Text:** 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,	No response needed

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0.5.	Mark W. LeChevallier, PhD	1B	251	**Excerpt Text:** 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.	No response needed
0.5.	Mark W. LeChevallier, PhD	1B	252	**Excerpt Text:** 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.	Hotlinks to every term in the EPA Thesaurus were not added. However a hotlink to the Thesaurus was added. The workgroup felt that expansion of the appendices was not warranted at this time.
0.5.	Mark W. LeChevallier, PhD	1C	253	**Excerpt Text:** 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.	No response needed

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0.5.	Patricia L. Meinhardt, MD, MPH	1A	291	**Excerpt Text:** 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.	No response needed.
0.5.	Patricia L. Meinhardt, MD, MPH	1A	292	**Excerpt Text:** 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.	No response needed.

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0.5.	Patricia L. Meinhardt, MD, MPH	1A	293	**Excerpt Text:** 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.	No response needed.
0.5.	Patricia L. Meinhardt, MD, MPH	1B	294	**Excerpt Text:** 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.	No response needed.

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0.5.	Patricia L. Meinhardt, MD, MPH	1D	297	**Excerpt Text:** 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.	No response needed.
0.5.	Christine L. Moe, PhD	1A	322	**Excerpt Text:** 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).	The workgroup believes the subheadings are helpful.
0.5.	Christine L. Moe, PhD	1B	323	**Excerpt Text:** 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".	We have provided a glossary and link to the EPA MRA Thesaurus. The workgroup recognizes that we cannot capture every term.

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0.5.	Christine L. Moe, PhD	1C	326	**Excerpt Text:** 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.	Examples and case studies were not added for two reasons. First, the workgroup found during development of the document that selection of case studies was very difficult and second, at this stage in development of the document, any new examples would not have been peer reviewed.
0.5.	Christine L. Moe, PhD	1D	327	**Excerpt Text:** 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).	How the guideline is compatible with WHO is discussed.
0.5.	Gary S. Sayler, PhD	1A	389	**Excerpt Text:** 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.	No response needed.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
0.5.	Gary S. Sayler, PhD	1B	391	**Excerpt Text:** 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.	Abbreviations were moved to the front of the document.
0.5.	Gary S. Sayler, PhD	1B	392	**Excerpt Text:** 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.	Chapter 3 was not divided into 2 chapters. Other reviewers did not suggest this and the workgroup felt the outline of the document is well crafted.
0.5.	Gary S. Sayler, PhD	1C	393	**Excerpt Text:** 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.	Expansion beyond food and water is beyond the scope of the document.
0.5.	Gary S. Sayler, PhD	1D	394	**Excerpt Text:** 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.	This is beyond the scope of the document.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
0.5.	Donald W. Schaffner, PhD	1A	423	**Excerpt Text:** 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.	The workgroup discussed the terms HC and DR modeling extensively and believe the way they are presented in the document is most useful. The details in chapters 4, 5, and 6 were maintained. Interaction between risk assessors and risk managers are presented in chapter 2 because it is most crucial during planning and scoping. Chapters 7 and 8 are more geared towards what risk assessors should know about risk management and risk communication.
0.5.	Donald W. Schaffner, PhD	1B	424	**Excerpt Text:** 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.	Section 1.2 was changed to "What are the Benefits of this Guideline?" and edited.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
0.5.	Donald W. Schaffner, PhD	1C	425	**Excerpt Text:** 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.	US regulatory environments differ from agency to agency. This is why risk assessors are first instructed to check with their agencies resources and policies. This guideline can then help fill gaps where risk assessors have leeway within the context of their agency.
0.5.	Donald W. Schaffner, PhD	1C	426	**Excerpt Text:** 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.	The introductory text has been revised.
1.	Tony Cox, Jr., PhD	2A	8	**Excerpt Text:** 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).	Chapter 1 has been shortened, by combining and editing overlapping questions. Sections 1.6 and 1.7 were merged into a new section 1.4. Sections 1.1, 1.3, and 1.8 were deleted.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
1.	Tony Cox, Jr., PhD	2B	9	**Excerpt Text:** 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.	Page 5 text was edited Page 19, 20, 21, 25 – the workgroup believes these points are valid. This type of information may not be as obvious as the review suggests.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
1.	Darrell W. Donahue, PhD	2A	48	**Excerpt Text:** 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.	An adaptation of NRC, 2009, S-1 was added to chapter 1.
1.	Joseph N.S. Eisenberg, PhD	2A	136	**Excerpt Text:** 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.	The document was revised to include references to existing guidelines.
1.	Joseph N.S. Eisenberg, PhD	2B	138	**Excerpt Text:** 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.	Section 1.3 was deleted.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
1.	Jeffrey K. Griffiths, MD, MPH	2A	192	**Excerpt Text:** 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.	No response needed.
1.	Jeffrey K. Griffiths, MD, MPH	2A	193	**Excerpt Text:** 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!).	The text has been edited to clarify that "typically" does not imply that investigation of long term effects should not be considered. "Unlike the long-term exposures often considered for chemicals, longer-term risks due to pathogen exposure have not typically been considered for MRA. However, as more information on sequelae becomes available they can be considered in MRA."
1.	Jeffrey K. Griffiths, MD, MPH	2B	194	**Excerpt Text:** 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.	The workgroup believes that urgency is important, but didn't want to highlight this as being a key difference between chemicals and microbes.
1.	Jeffrey K. Griffiths, MD, MPH	2B	206	**Excerpt Text:** Balance of chapter – no comments except perhaps section 1.9 moving to Preface.	Section 1.9 is now Section 1.5

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
1.	Mark W. LeChevallier, PhD	2B	256	**Excerpt Text:** 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).	The iterative nature of risk assessment has been added to section 6.0 and section 7.2.
1.	Patricia L. Meinhardt, MD, MPH	2A	298	**Excerpt Text:** 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.	No response needed
1.	Patricia L. Meinhardt, MD, MPH	2B	299	**Excerpt Text:** 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).	Chapter 1 has been reorganized. However the differences between microbes and chemicals are still fairly early in the chapter because of its importance. Section 1.6 has been combined with section 1.7 and moved into a new section 1.4.
1.	Christine L. Moe, PhD	2A	328	**Excerpt Text:** 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: **Image 328 shown below**	In general illustrations were not added because of the timeline and budget required to create illustrations according to government publication guidelines.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
1.	Christine L. Moe, PhD	2B	331	**Excerpt Text:** 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).	These edits were made. The second person perspective was maintained. An explanation was added – "When reading through this guideline, the format is in a question and answer format. The question may be thought of as the risk assessor asking a specific question (the use of "I" in many instances). The answer is a response to the assessor's question (the use of "you" refers back to the risk assessor)."
1.	Gary S. Sayler, PhD	1B	390	**Excerpt Text:** 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.	No response needed
1.	Gary S. Sayler, PhD	2A	395	**Excerpt Text:** 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)	Added section titled "Who is this guide written for?" (new section 1.1)

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
1.	Gary S. Sayler, PhD	2B	400	**Excerpt Text:** 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?	Section 1.1 was deleted.
1.	Donald W. Schaffner, PhD	2B	429	**Excerpt Text:** 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.	Figure 1.1 was deleted. Section 1.5 was moved to section 1.3. Sections 1.6, and 1.7 were combined and moved to section 1.4. The overall material for these sections was important to include.
1.	Donald W. Schaffner, PhD	-	450	**Excerpt Text:** Page 7: Content: "INTERAGENCY WORKGROUP MEMBERS" Comment: Why no FDA involvement? CVM and CFSAN have both done microbial risk assessments.	CFSAN and CVM are on the Interagency Risk Assessment Consortium, which reviewed this document. In addition CFSAN provided comments during interagency review.
1.1.	Joseph N.S. Eisenberg, PhD	2B	137	**Excerpt Text:** 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]	In government documents it is customary to write out titles for other government documents. The references were not moved to footnotes.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
1.1.	Gary S. Sayler, PhD	2A	396	**Excerpt Text:** 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?	Figure 1.1 and section 1.1 have been deleted.
1.1.	Donald W. Schaffner, PhD	2A	451	**Excerpt Text:** 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.	Figure 1.1 was deleted and replaced with a different figure.
1.2.	Donald W. Schaffner, PhD	2A	452	**Excerpt Text:** 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	These references were added to this section.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
1.3.	Jeffrey K. Griffiths, MD, MPH	1C	191	**Excerpt Text:** 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.	Text has been edited – "The agencies that regulate food and environmental contaminants recognize that the ultimate sources of pathogens are the same for different media (e.g., water and food). Because the health effects and dose-response relationships are similar regardless of media for many of the pathogens, it is useful to have common principles and approaches to assess risks across media and exposure settings."
1.3.	Mark W. LeChevallier, PhD	1D	254	**Excerpt Text:** 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.	The word "all" was deleted.
1.3.	Donald W. Schaffner, PhD	2A	453	**Excerpt Text:** 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?	CFSAN and CVM are on the Interagency Risk Assessment Consortium, which reviewed this document. In addition CFSAN provided comments during interagency review.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
1.4.	Gary S. Sayler, PhD	2A	397	**Excerpt Text:** 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.	Section 1.4 has been re-written. Life Stages is the EPA terminology and is explained in the footnote. The workgroup believes the discussion that includes "submicrobial," "sensitive," and "susceptibility" is clear. The terms sensitive, susceptible, and vulnerable are all used to describe similar attributes of populations, however, some authors have made distinctions among these terms. For example, sensitive could result from behavioral traits, susceptible refers to immune related characteristics, and vulnerable can encompass both these.
1.5.	Jeffrey K. Griffiths, MD, MPH	2B	195	**Excerpt Text:** 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.	Examples and case studies were not added for two reasons. First, the workgroup found during development of the document that selection of case studies was very difficult and second, at this stage in development of the document, any new examples would not have been peer reviewed.
1.5.	Jeffrey K. Griffiths, MD, MPH	2B	196	**Excerpt Text:** 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.	Text added – "These toxins cause many of the symptoms of GI illness."

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
1.5.	Jeffrey K. Griffiths, MD, MPH	2B	197	**Excerpt Text:** 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.	Text added – "Other factors that influence susceptibility but not necessarily through changes in immunity include concomitant illnesses and medications."
1.5.	Jeffrey K. Griffiths, MD, MPH	2B	198	**Excerpt Text:** 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.	These examples were added.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
1.5.	Jeffrey K. Griffiths, MD, MPH	2B	199	**Excerpt Text:** 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 (R0) 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.	Text edited – "Microorganisms are genetically diverse and allelic ratios (variations of the same gene) in a population can change significantly within a few generations." The level of detail suggested is not needed for this particular paragraph. More in depth and updated discussion of secondary spread was added elsewhere in the document.
1.5.	Jeffrey K. Griffiths, MD, MPH	2B	200	**Excerpt Text:** 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.	Text added – "The matrix (all the components of the media, e.g. particles, pH) can influence the spatial distribution of microorganisms."

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
1.5.	Jeffrey K. Griffiths, MD, MPH	2B	201	**Excerpt Text:** 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.	The text has been edited to clarify that "typically" does not imply that investigation of long term effects should not be considered. "Unlike the long-term exposures often considered for chemicals, longer-term risks due to pathogen exposure have not typically been considered for MRA. However, as more information on sequelae become available it can be considered in MRA."
1.5.	Jeffrey K. Griffiths, MD, MPH	2B	203	**Excerpt Text:** 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.	Pointing out specific shortcomings of previous risk assessments is beyond the scope of this document.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
1.5.	Jeffrey K. Griffiths, MD, MPH	2B	204	**Excerpt Text:** 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.	Text added to section 3.7 – "You should be aware that techniques and methods change, so staying up to date on the current status of different methods is important." Population dynamics is discussed in section 5.2.7. Also text added to section 1.3 – "For some pathogens population dynamics are better characterized than for other pathogens, so information may be available or not."
1.5.	Jeffrey K. Griffiths, MD, MPH	2B	205	**Excerpt Text:** 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.	Text added to section 1.3 – "Some organisms can be transmitted via one route of exposure and then transmitted to secondary hosts via a different route, such as oral ingestion of a virus leading to spread by respiratory droplets." The workgroup believes aspects of this have been captured.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
1.5.	Mark W. LeChevallier, PhD	1D	255	**Excerpt Text:** 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.	Text added to section 1.3 – "In addition, environmental stresses can impact the virulence of some pathogens."
1.5.	Gary S. Sayler, PhD	2B	398	**Excerpt Text:** 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?	Because of the importance of the material, the discussion was maintained in chapter 1 and not moved to an appendix.
1.6.	Christine L. Moe, PhD	2B	329	**Excerpt Text:** 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 1.6 title has been deleted and the text merged into a new section 1.4.
1.6.	Gary S. Sayler, PhD	2B	399	**Excerpt Text:** 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.	The epi triad is a well known and accepted model for investigation of disease.
1.7.	Donald W. Schaffner, PhD	2A	454	**Excerpt Text:** 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.	The workgroup decided to maintain the second person perspective.
1.8.	Donald W. Schaffner, PhD	2A	455	**Excerpt Text:** 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…"	"With my agencies" is first person perspective, which is how the questions are written. The answers to the questions in the document are in second person perspective because it addresses the reader.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
1.10.	Tony Cox, Jr., PhD	1D	6	**Excerpt Text:** 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.	The workgroup tried to use common usage language. These terms have been used in guidelines to demonstrate flexibility.
1.10.	Tony Cox, Jr., PhD	1D	7	**Excerpt Text:** Chapter 1: 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.	Text added: "By addressing these principles and adhering to well established scientific processes such as peer review, the correctness and the real world applicability of the MRA is most likely ensured." The TCCR criteria from the EPA Risk Characterization Handbook were further edited.
1.10.	Darrell W. Donahue, PhD	2B	49	**Excerpt Text:** 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.	The Codex principles have been edited/adapted to make them more concise.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
1.10.	Christine L. Moe, PhD	2B	330	**Excerpt Text:** 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.	The workgroup wanted to maintain clear presentation of material from different sources. Editing material from other sources to synthesize was deemed unnecessary.
2.	Tony Cox, Jr., PhD	3A	10	**Excerpt Text:** 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).	References to support why planning and scoping are important have been added. When planning and scoping are done well, the practical relevance of the MRA is of key importance. Planning and scoping can either result in focusing on a subset of strains, or may result in a broader investigation.
2.	Tony Cox, Jr., PhD	3A	14	**Excerpt Text:** 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.	Description of screening risk assessment was added to section 1.8.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
2.	Tony Cox, Jr., PhD	3C	15	**Excerpt Text:** 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.	Text has been added to section 2.2 and 2.3 to address these potential pitfalls.
2.	Darrell W. Donahue, PhD	3B	66	**Excerpt Text:** Response: This chapter addresses the needs of the stakeholders who may read the Guideline.	No response needed
2.	Darrell W. Donahue, PhD	3C	67	**Excerpt Text:** Response: The suggestions given in the 3A response above are provided to increase the overall readability of the document.	No response needed
2.	Joseph N.S. Eisenberg, PhD	3A	139	**Excerpt Text:** 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.	No response needed
2.	Joseph N.S. Eisenberg, PhD	3B	140	**Excerpt Text:** This chapter addresses the needs of the stakeholders involved.	No response needed

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
2.	Joseph N.S. Eisenberg, PhD	3C	141	**Excerpt Text:** The structure of this chapter needs work. More synthesis is necessary and many sections don't seem to belong in this chapter.	The workgroup wanted to maintain clear presentation of material from different sources. Editing material from other sources to synthesize was deemed unnecessary.
2.	Joseph N.S. Eisenberg, PhD	3C	143	**Excerpt Text:** 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 2.3 was edited, but remains because deciding to initiate is part of planning and scoping. Section 2.5 was moved to Section 1.7. Section 2.8 was deleted.
2.	Jeffrey K. Griffiths, MD, MPH	3C	207	**Excerpt Text:** 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.	The workgroup believes that the paragraph the reviewer refers to is adequate to frame stakeholder involvement.
2.	Mark W. LeChevallier, PhD	3A	257	**Excerpt Text:** 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.	No response needed
2.	Mark W. LeChevallier, PhD	3B	258	**Excerpt Text:** Yes, I think it well addresses the needs of the stakeholders (e.g., risk assessor, risk manager/decision-maker, and interested parties).	No response needed

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
2.	Patricia L. Meinhardt, MD, MPH	3A	300	**Excerpt Text:** 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.	No response needed
2.	Patricia L. Meinhardt, MD, MPH	3B	301	**Excerpt Text:** 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.	No response needed
2.	Patricia L. Meinhardt, MD, MPH	3C	303	**Excerpt Text:** 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.	No response needed
2.	Christine L. Moe, PhD	3A	332	**Excerpt Text:** 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.	Section 2.4 was moved to Section 2.6. Section 2.5.3 on threat and vulnerability assessments was condensed into one paragraph and added to the list of types of MRA in section 1.8.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
2.	Christine L. Moe, PhD	3B	333	**Excerpt Text:** Not my area of expertise.	No response needed
2.	Christine L. Moe, PhD	3C	334	**Excerpt Text:** 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.	The definition of planning and scoping is in section 2.1. In government documents it is customary to write out titles for other government documents. The references were not moved to a separate section.
2.	Christine L. Moe, PhD	3C	335	**Excerpt Text:** 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?	For MRA selecting a representative example can be too limiting. We have added an example of a conceptual model. Several of the lists were moved to text boxes.
2.	Gary S. Sayler, PhD	3A	401	**Excerpt Text:** This chapter appears rather comprehensive in laying out the rationale, needs and approaches for planning and scoping activities.	No response needed
2.	Gary S. Sayler, PhD	3B	402	**Excerpt Text:** Stakeholder involvement and needs appear well accommodated.	No response needed
2.	Donald W. Schaffner, PhD	3A	430	**Excerpt Text:** 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.	Section 2.5.3 on threat and vulnerability assessments was condensed into one paragraph and added to the list of types of MRA in section 1.8.
2.	Donald W. Schaffner, PhD	3B	431	**Excerpt Text:** The document does appear to address the needs of all those listed.	No response needed

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
2.1.	Darrell W. Donahue, PhD	3A	51	**Excerpt Text:** 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".	Text added to section 2.1 – "Identifying initial risk management options that are available" NRC 2009 citation added.
2.1.	Joseph N.S. Eisenberg, PhD	3C	142	**Excerpt Text:** 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.	Section 2.1.1 was edited and moved to section 2.2. Section 2.2 was merged into section 2.1. Text was edited to make these definitions clear.
2.1.	Mark W. LeChevallier, PhD	3C	259	**Excerpt Text:** Page 16, line 2. Provide text for abbreviation CFSAN.	Text edited.
2.1.	Donald W. Schaffner, PhD	3C	456	**Excerpt Text:** 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.	CFSAN provided comments during interagency review.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
2.1.1.	Tony Cox, Jr., PhD	3A	11	**Excerpt Text:** 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.	Text added to section 2.2 "unintended consequences should be identified where possible and addressed as part of the scope of the MRA (e.g., do possible interventions targeted at reducing one pathogen run the risk of increasing illnesses from another pathogen)"
2.1.1.	Tony Cox, Jr., PhD	3A	12	**Excerpt Text:** 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).	Text added to section 2.2 "In some cases, a valid conceptual model may be unavailable, or there may be multiple plausible, but distinct conceptual models. The validity of a selected conceptual model may simply be uncertain. You should be aware of these possibilities and may need to consider multiple (and uncertain) conceptual models and possibly model-free (e.g., source tracking) methods as part of the formulation."
2.1.1.	Darrell W. Donahue, PhD	3A	52	**Excerpt Text:** 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.	Section 2.1.1 was moved to section 2.2 and the old section 2.2 was merged into 2.1
2.2.	Tony Cox, Jr., PhD	3C	16	**Excerpt Text:** 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.)	Text has been added to section 2.2 and 2.3 to address these potential pitfalls.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
2.2.	Darrell W. Donahue, PhD	3A	53	**Excerpt Text:** P. 17, line 10, "better informed decisions with stakeholder buy-in. – add this for succinctness.	Text edited – "f) better informed decisions with stakeholder buy-in"
2.3.	Tony Cox, Jr., PhD	3C	17	**Excerpt Text:** 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.'	The workgroup tried to use common usage language. These terms have been used in guidelines to demonstrate flexibility.
2.3.	Tony Cox, Jr., PhD	3C	18	**Excerpt Text:** 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.) **Excerpt References:** Cox LA Jr. What's wrong with hazard-ranking systems? An expository note. Risk Analysis. 2009 Jul;29(7):940-8.	VOI section has been edited. Whether to initiate a risk assessment is a policy decision that a risk assessor will probably not make. The information on initiating risk assessments is provided as general information for risk assessors to understand the overall process. Each agency has their own processes for making these decisions and risk assessors should be familiar with that process. It is beyond the scope of this document to comment on agency processes for deciding to conduct MRA.
2.3.	Mark W. LeChevallier, PhD	3C	260	**Excerpt Text:** 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.	Text added – "Determining data gaps and the relative importance of different data gaps will progress iteratively as the risk assessment is conducted iteratively."
2.4.	Patricia L. Meinhardt, MD, MPH	3B	302	**Excerpt Text:** 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.	No response needed.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
2.5.1	Darrell W. Donahue, PhD	3A	54	**Excerpt Text:** Section 2.5.1 – need to use subtitles in this section for different "depths" to make it clear that there are different depths/levels. Section 2.5.1, p. 22, Lines 23-28 – need to finish with tying these comments back into relating it to planning and scoping.	Section 2.5.1 was moved to section 2.3
2.5.2	Tony Cox, Jr., PhD	3C	19	**Excerpt Text:** 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).	Description of screening risk assessment was added to section 1.8.
2.5.2	Darrell W. Donahue, PhD	3A	55	**Excerpt Text:** Section 2.5.2 – make sure subsection titles that follow are the same as the examples list in lines 33-34, p. 22.	Section 2.5.2 was edited and moved to section 1.8.
2.5.2	Jeffrey K. Griffiths, MD, MPH	3C	208	**Excerpt Text:** 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.	Text added to section 3.11 – "There are also longer term changes that influence microorganism dynamics and occurrence in the environment. For example, seasonal changes, climate change, habitat changes, and urban environments can all impact microbial dynamics. Some risk assessment scenarios may include the impacts of these longer term factors."

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
2.5.3	Tony Cox, Jr., PhD	3C	20	**Excerpt Text:** 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.) **Excerpt References:** 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.)	Section 2.5.3 on threat and vulnerability assessments was condensed into one paragraph and added to the list of types of MRA in section 1.8.
2.5.3	Darrell W. Donahue, PhD	3A	56	**Excerpt Text:** Need a conclusion section (near p. 25, line 27) that draws the conclusion of section 2.5 – answering the "so what" question.	A summary was added (section 2.6)
2.5.3	Gary S. Sayler, PhD	3C	403	**Excerpt Text:** 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 2.5.3 on threat and vulnerability assessments was condensed into one paragraph and added to the list of types of MRA in section 1.8.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
2.5.3	Donald W. Schaffner, PhD	3C	432	**Excerpt Text:** Delete the CARVER+Shock section to simply the mention of a reference.	Section 2.5.3 on threat and vulnerability assessments was condensed into one paragraph and added to the list of types of MRA in section 1.8.
2.6.	Tony Cox, Jr., PhD	3C	21	**Excerpt Text:** 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.	The workgroup feels that more detail is needed than quick practical advice. In the past planning and scoping has been a less prominent feature in frameworks. However the workgroup believes that a large portion of the effort in MRA is actually in the planning and scoping.
2.6.	Darrell W. Donahue, PhD	3A	57	**Excerpt Text:** P. 27, line 16 – be consistent with term usage (see p. 22, line 33-34).	The list in section 2.4 has been edited to match the list in section 1.8.
2.6.	Joseph N.S. Eisenberg, PhD	3C	144	**Excerpt Text:** 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 has been moved to section 2.4. The text box and list in the main text do not need to match exactly. Some activities do not have deliverables. Text has been added to section 2.4 to explain the products and activities/elements of planning and scoping. The products listed in the text box are underlined as they occur in relation to the description of the activities/elements.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
2.6.	Jeffrey K. Griffiths, MD, MPH	3C	209	**Excerpt Text:** 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.	Taxon has been added to the glossary.
2.6.	Jeffrey K. Griffiths, MD, MPH	3C	210	**Excerpt Text:** 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.	This is a policy call depending on existing statutory mandate for each Agency. Stakeholder involvement is addressed elsewhere.
2.6.	Gary S. Sayler, PhD	3C	404	**Excerpt Text:** Section 2.6 appears rather central to Scoping and should be moved forward in the chapter.	Section 2.6 has been moved up to section 2.4
2.6.1.	Darrell W. Donahue, PhD	3A	58	**Excerpt Text:** P. 29, line 25 – this reference to section 2.4 does not seem to match up, should it be "earlier in section 2.6".	Text added – "This section begins with an overview of the elements and activities of planning and scoping, then provides more detail for selected elements as third level header questions and answers."
2.6.2.	Gary S. Sayler, PhD	3C	405	**Excerpt Text:** 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)	Risk profile is a term that has been used in different contexts and is very important internationally. The workgroup believes it is important to keep this section in the document.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
2.6.3.	Tony Cox, Jr., PhD	3C	22	**Excerpt Text:** 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.	Text added to section 2.2 "In some cases, a valid conceptual model may be unavailable, or there may be multiple plausible, but distinct conceptual models. The validity of a selected conceptual model may simply be uncertain. You should be aware of these possibilities and may need to consider multiple (and uncertain) conceptual models and possibly model-free (e.g., source tracking) methods as part of the formulation."
2.6.3.	Darrell W. Donahue, PhD	3A	59	**Excerpt Text:** 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.	Text added – "Overall the purpose of a conceptual model is to enhance the documentation of the risk assessment, so that readers will have a clearer picture of the risk assessment." An example conceptual model was added.
2.6.4.	Tony Cox, Jr., PhD	3A	13	**Excerpt Text:** 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 analysis plan is not restricted to a pathway-based approach.
2.6.4.	Tony Cox, Jr., PhD	3C	23	**Excerpt Text:** 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.	The concept of an analysis plan can be interpreted broadly according to agency needs, so details are really necessary. The point is that plans should be put on paper.
2.6.4.	Darrell W. Donahue, PhD	3A	60	**Excerpt Text:** Consider reversing sections 2.6.4 and 2.6.5 for better readability and flow	Sections 2.6.4 and 2.6.5 were reversed in order.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
2.6.5.	Tony Cox, Jr., PhD	3C	24	**Excerpt Text:** 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.	The workgroup believes that ranking data gaps for the purpose of prioritizing resources devoted to filling data gaps is important. Text regarding VOI has been edited.
2.6.5.	Tony Cox, Jr., PhD	3C	25	**Excerpt Text:** 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 sentence "If no other empiric evidence is available, expert judgment may offer the best available science to inform a model." Has been edited to: "If no other empiric evidence is available, expert judgment may offer insights to inform a model for example."

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
2.6.5.	Tony Cox, Jr., PhD	3C	26	**Excerpt Text:** 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.	The example of PM2.5 has been removed.
2.6.5.	Tony Cox, Jr., PhD	3C	27	**Excerpt Text:** 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.	The section on expert elicitation has been edited to contain much less detail.
2.6.5.	Jeffrey K. Griffiths, MD, MPH	3C	211	**Excerpt Text:** 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.	Response not needed
2.6.6.	Tony Cox, Jr., PhD	3C	28	**Excerpt Text:** Section 2.6.6 has some valuable ideas.	Response not needed

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
2.6.6.	Darrell W. Donahue, PhD	3A	61	**Excerpt Text:** 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.	This section was not shortened. Data quality is very important to the federal government. OMB specifically commented on the content in this section.
2.6.6.	Joseph N.S. Eisenberg, PhD	3C	145	**Excerpt Text:** 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.	This section was not shortened. Data quality is very important to the federal government. OMB specifically commented on the content in this section.
2.6.6.	Jeffrey K. Griffiths, MD, MPH	3C	212	**Excerpt Text:** 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.	Decision making in the absence of perfect information has been addressed in screening risk assessment and use of default assumptions. The usual practice for risk assessment is to use the best available data.
2.6.6.	Gary S. Sayler, PhD	3C	406	**Excerpt Text:** 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.	Data quality is very important to the federal government. OMB specifically commented on the content in this section. This is not a sidebar, footnote, or appendix, it is of central importance for government risk assessors.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
2.6.7.	Tony Cox, Jr., PhD	3C	29	**Excerpt Text:** 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 phrase taken out of context. It does not apply to the VOI framework itself, but why you would need VOI.
2.6.7.	Tony Cox, Jr., PhD	3C	30	**Excerpt Text:** 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).	The section on VOI has been edited and shortened.
2.6.7.	Darrell W. Donahue, PhD	3A	62	**Excerpt Text:** 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.	The section on VOI has been edited and shortened.
2.6.8.	Darrell W. Donahue, PhD	3A	63	**Excerpt Text:** Section 2.6.8, p. 39, lines 10-14 – please reverse the order of a) and b) to make readability more clear.	For communications plans stakeholders should be identified before communication goals. Goals may be different for different stakeholders.
2.7.	Darrell W. Donahue, PhD	3A	64	**Excerpt Text:** Section 2.7, p. 40, lines 5-6 – policy choices should also be identified to the best available information during planning and scoping.	Section 2.7 has been moved to section 1.9 and edited.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
2.7.	Joseph N.S. Eisenberg, PhD	3C	146	**Excerpt Text:** I don't really understand section 2.7, and it is not made clear why it belongs in this chapter.	Section 2.7 has been moved to section 1.9 and edited.
2.8.	Darrell W. Donahue, PhD	3A	65	**Excerpt Text:** 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.	New section 2.6 is a summary.
3.	Tony Cox, Jr., PhD	4B	31	**Excerpt Text:** 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.	The discussion of hazard has been edited for clarity.
3.	Darrell W. Donahue, PhD	4A	68	**Excerpt Text:** 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).	The text explains why these two terms were combined.
3.	Darrell W. Donahue, PhD	4B	69	**Excerpt Text:** 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."	The text explains why these two terms were combined. This approach also improves the description of the hazard.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
3.	Joseph N.S. Eisenberg, PhD	4A	147	**Excerpt Text:** 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.	Both the text and a footnote now explain why these two terms were combined. Table 3.1 is not meant to be comprehensive. Readers are referred to ASM's Manual of Clinical Microbiology. Adding a table of detection methods is beyond the scope
3.	Joseph N.S. Eisenberg, PhD	4B	148	**Excerpt Text:** 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.	The workgroup decided to retain the original format based on the reasoning described at the beginning of chapter 3.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
3.	Jeffrey K. Griffiths, MD, MPH	4A	213	**Excerpt Text:** 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.	Section 3.1 What are Hazard Identification and Hazard Characterization? Explains HI and HC.
3.	Jeffrey K. Griffiths, MD, MPH	4B	214	**Excerpt Text:** 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.	Section 3.1 What are Hazard Identification and Hazard Characterization? Explains HI and HC.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
3.	Mark W. LeChevallier, PhD	4A	261	**Excerpt Text:** 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 of 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.	The term hazard has been clarified.
3.	Mark W. LeChevallier, PhD	4B	262	**Excerpt Text:** Agreed that combining hazard identification and characterization is useful and logical.	No response needed.
3.	Patricia L. Meinhardt, MD, MPH	4A	304	**Excerpt Text:** 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.	No response needed.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
3.	Patricia L. Meinhardt, MD, MPH	4B	305	**Excerpt Text:** 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.	No response needed.
3.	Patricia L. Meinhardt, MD, MPH	4B	306	**Excerpt Text:** 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.	No response needed.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
3.	Christine L. Moe, PhD	4A	336	**Excerpt Text:** • 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.	The workgroup feels the level of technical information is appropriate.
3.	Christine L. Moe, PhD	4B	337	**Excerpt Text:** Need to clarify when discussing detection of microorganism in human clinical specimens vs. environmental samples	Text added – "In some cases clinical specimens from human cases may have more specific typing information, whereas environmental samples may be evaluated with methods that detect and quantify a different subtype, or a broader group. The MRA documentation should include information on what level of pathogen characterization is relevant for each data set used. For example, if dose-response data is from one isolate (e.g., human trials with specific isolates of *Cryptosporidium*) and environmental occurrence data includes a broader set (e.g., *Cryptosporidium* counted by microscopy) the limitations of assumptions that are made when both these types of data are used in the same risk assessment, should be transparently discussed."

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
3.	Gary S. Sayler, PhD	4A	407	**Excerpt Text:** 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.	The term hazard has been clarified.
3.	Gary S. Sayler, PhD	4B	408	**Excerpt Text:** 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 ….."	HI and HC are not considered 2 distinct elements. They are both qualitative attributes of the hazard. Text edited to – "One such mechanism is the horizontal transfer of genes within and between viral and bacterial strains."
3.	Donald W. Schaffner, PhD	4A	433	**Excerpt Text:** 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.	Section 3.1 What are Hazard Identification and Hazard Characterization? Explains HI and HC.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
3.	Donald W. Schaffner, PhD	4A	434	**Excerpt Text:** 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.	These are attributes that are important for understanding pathogens. Not all pathogens have these characteristics that would be relevant in the context of MRA, but sometime not including this information can be a blind spot in the MRA. This type of information may need to be considered in MRA.
3.	Donald W. Schaffner, PhD	4B	435	**Excerpt Text:** 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.	Section 3.1 What are Hazard Identification and Hazard Characterization? Explains HI and HC.
3.	Donald W. Schaffner, PhD	4	457	**Excerpt Text:** 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.	Correct, the workgroup considers the dose-response assessment to be quantitative and the term hazard characterization to be the qualitative part of describing the organism.
3.1.	Darrell W. Donahue, PhD	4B	70	**Excerpt Text:** 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.	Edited as suggested.
3.1.	Jeffrey K. Griffiths, MD, MPH	4B	215	**Excerpt Text:** 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.	Taxon has been added to the glossary.
3.1.	Donald W. Schaffner, PhD	4	458	**Excerpt Text:** 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.	The agent is a microorganism, but a hazard can be broader than an agent. The idea is that a risk assessment could be done to assess the risk of days spent in a hospital. This is a bit more out of the box than most MRAs, but still possible within the MRA framework.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
3.2.	Darrell W. Donahue, PhD	4B	71	**Excerpt Text:** 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.	The workgroup feels this is unnecessary because the document may be read in a non-linear manner. Text linking sections is not as important in the question and answer format.
3.2.	Donald W. Schaffner, PhD	4	459	**Excerpt Text:** Page 52: Content: "What are Hazard Identification and Hazard Characterization?" Comment: It seems like this section should come first in the chapter.	The workgroup felt that defining hazard first was important. However the last paragraph of section 3.2 has been moved to the introduction to chapter 3.
3.3.	Darrell W. Donahue, PhD	4B	72	**Excerpt Text:** P. 45-46 need to reformat this itemized listing. P. 46, line 17-18, Host characterization is as important as the "omic" techniques/technologies listed here…consider reversing order of this listing.	The "omics" are important for both host and hazard characterization. In this context the "omics" support host characterization.
3.3.	Jeffrey K. Griffiths, MD, MPH	4B	216	**Excerpt Text:** 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 random sampling – 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}.	Text changed to – "the ability to degrade and migrate through the extracellular matrix and invade the host cells" The definition of genetic drift has been changed to – "random fluctuations in the frequency of alleles in a small isolated population, presumably owing to chance rather than natural selection"

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
3.4.	Mark W. LeChevallier, PhD	4B	263	**Excerpt Text:** 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.	Edit made
3.5.	Jeffrey K. Griffiths, MD, MPH	4B	217	**Excerpt Text:** 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.	Although this comment is technically correct the suggested edit is not as smooth as the commonly used phrase "Biotechnology takes advantage of…", which is the new text edit.
3.5.	Jeffrey K. Griffiths, MD, MPH	4B	218	**Excerpt Text:** Page 48 lines 37-38 – define superantigens, quorum sensing if you mention them here, and include in the glossary.	Superantigen and quorum sensing were added to the glossary.
3.5.	Donald W. Schaffner, PhD	4	460	**Excerpt Text:** 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.	These are attributes that are important for understanding pathogens. Not all pathogens have these characteristics that would be relevant in the context of MRA, but sometime not including this information can be a blind spot in the MRA. This type of information may need to be considered in MRA.
3.6.	Jeffrey K. Griffiths, MD, MPH	4B	219	**Excerpt Text:** 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.	The microorganisms were re-ordered and the suggested organisms were added.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
3.6.	Donald W. Schaffner, PhD	4	461	**Excerpt Text:** 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.	Batz et al., 2011 and Scallan et al., 2011 papers have been added.
3.7.	Jeffrey K. Griffiths, MD, MPH	4B	220	**Excerpt Text:** 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).	PCR and concentration of water samples was added.
3.7.	Donald W. Schaffner, PhD	4	462	**Excerpt Text:** Page 60: Content: "You should be familiar with laboratory approaches for identifying and quantifying the microorganism(s) of concern." Comment: Why?	Text edited to "you should become familiar…"

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
3.8.	Mark W. LeChevallier, PhD	4B	264	**Excerpt Text:** 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.	Text added to section 3.8 – "In some cases clinical specimens from human cases may have more specific typing information, whereas environmental samples may be evaluated with methods that detect and quantify a different subtype, or a broader group. The MRA documentation should include information on what level of pathogen characterization is relevant for each data set used. For example, if dose-response data is from one isolate (e.g., human trials with specific isolates of *Cryptosporidium*) and environmental occurrence data includes a broader set (e.g., *Cryptosporidium* counted by microscopy) the limitations of assumptions that are made when both these types of data are used in the same risk assessment, should be transparently discussed."
3.8.	Mark W. LeChevallier, PhD	4B	265	**Excerpt Text:** 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.	Edited – "easily" added Text added – "In addition, disinfectants and processing (e.g., heat) can also stress microbes and may be a factor that needs to be considered, when processes are included in the risk assessment scenario."
3.9.	Darrell W. Donahue, PhD	4B	73	**Excerpt Text:** P. 56, section 3.9, line 46 – should briefly intro the idea of sensitive sub populations here.	Text added – "Some of the factors listed below are sometimes the defining characteristic of subpopulations that may be explicitly addressed in the risk assessment."

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
3.9.	Jeffrey K. Griffiths, MD, MPH	4B	221	**Excerpt Text:** 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.	Text added – "The fact that all people pass through infancy and many through pregnancy and old age means that all people are relatively more susceptible at one time or another."
3.10.	Darrell W. Donahue, PhD	4B	74	**Excerpt Text:** P. 58, section, 3.10. This section is really a part of section 3.9 and should be treated as such.	The work group feels that lifestage is important enough that it deserves a separate question.
3.11.	Darrell W. Donahue, PhD	4B	75	**Excerpt Text:** P. 60, bottom – again, a short paragraph to conclude chap 3 is needed here.	A summary for chapter 3 has been added.
3.11.	Mark W. LeChevallier , PhD	4B	266	**Excerpt Text:** 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.	Text added – "There are also longer term changes that influence microorganism dynamics and occurrence in the environment. For example, seasonal changes, climate change, habitat changes, and urban environments can all impact microbial dynamics. …"
4.	Darrell W. Donahue, PhD	5A	76	**Excerpt Text:** 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.	No response needed.
4.	Darrell W. Donahue, PhD	5B	85	**Excerpt Text:** 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.	Text edited in 4.2.1 to make this point.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
4.	Joseph N.S. Eisenberg, PhD	5A	149	**Excerpt Text:** 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.	Text added to include the caveat on narrow population group in section 4.2.1 Text edited to address this comment on epidemiologic data in section 4.1.3

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
4.	Joseph N.S. Eisenberg, PhD	5B	150	**Excerpt Text:** 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. **Excerpt References:** 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.	Section 4.1.4 edited to make this point and all recommended citations were added.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
4.	Joseph N.S. Eisenberg, PhD	5B	151	**Excerpt Text:** 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 **Excerpt References:** 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	Citations added as suggested.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
4.	Joseph N.S. Eisenberg, PhD	5B	152	**Excerpt Text:** 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. **Excerpt References:** 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.	Citations added as suggested.
4.	Joseph N.S. Eisenberg, PhD	5C	153	**Excerpt Text:** This is out of my field of expertise.	No response needed.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
4.	Jeffrey K. Griffiths, MD, MPH	5A	223	**Excerpt Text:** 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.	Cross references added as suggested.
4.	Jeffrey K. Griffiths, MD, MPH	5B	224	**Excerpt Text:** Not aware of any others; may be outside my expertise.	No response needed.
4.	Jeffrey K. Griffiths, MD, MPH	5C	225	**Excerpt Text:** 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.	As indicated by the reviewer, acquiring this information would be resource intensive. The timeline and budget do not permit the suggested literature review to be performed.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
4.	Jeffrey K. Griffiths, MD, MPH	5C	226	**Excerpt Text:** 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).	Most of the provided text has been included in section 4.1.3.
4.	Jeffrey K. Griffiths, MD, MPH	5C	227	**Excerpt Text:** 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.	Most of the provided text has been included in section 4.1.3.
4.	Jeffrey K. Griffiths, MD, MPH	5C	228	**Excerpt Text:** 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.	Most of the provided text has been included in section 4.1.3.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
4.	Jeffrey K. Griffiths, MD, MPH	5D	229	**Excerpt Text:** 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 (ID50) 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.	Where practical an additional illustration was added (see chapter 1).
4.	Mark W. LeChevallier, PhD	5A	267	**Excerpt Text:** 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.	No response needed.
4.	Mark W. LeChevallier, PhD	5C	268	**Excerpt Text:** 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.	The new text in section 4.1.3 addresses this perspective and comment.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
4.	Mark W. LeChevallier, PhD	5D	269	**Excerpt Text:** 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.	Text edited in section 4.2.4 to address this comment.
4.	Patricia L. Meinhardt, MD, MPH	5A	307	**Excerpt Text:** 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.	No response needed.
4.	Patricia L. Meinhardt, MD, MPH	5B	308	**Excerpt Text:** As an occupational and environmental medicine physician, addressing this question is outside of my area of expertise and I offer no response.	No response needed.
4.	Patricia L. Meinhardt, MD, MPH	5C	309	**Excerpt Text:** As an occupational and environmental medicine physician, addressing this question is outside of my area of expertise and I offer no response.	No response needed.
4.	Patricia L. Meinhardt, MD, MPH	5D	310	**Excerpt Text:** 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.	No response needed.
4.	Christine L. Moe, PhD	5A	338	**Excerpt Text:** Overall, this chapter is well written, and the material is presented at an appropriate level.	No response needed.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
4.	Christine L. Moe, PhD	5D	350	**Excerpt Text:** 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.	Text edited in Section 4.2.4 to address this comment Text edited in Section 4.2.5 to address this comment
4.	Christine L. Moe, PhD	5D	351	**Excerpt Text:** • 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. **Excerpt References:** 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.	Text edited in Section 4.2.4 to address this comment

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
4.	Christine L. Moe, PhD	5D	352	**Excerpt Text:** •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.	Text edited in Section 4.1.3 to address this comment Text edited in Section 4.2.4 to address this comment
4.	Gary S. Sayler, PhD	5A	409	**Excerpt Text:** 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.	No response needed.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
4.	Gary S. Sayler, PhD	5A	410	**Excerpt Text:** 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.	The text was edited in section 4.1.2 to address this comment. The title was also changed.
4.	Gary S. Sayler, PhD	5D	412	**Excerpt Text:** 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.	No response needed.
4.	Donald W. Schaffner, PhD	5A	436	**Excerpt Text:** 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.	No changes made. Other reviewers commented that the noted section was useful.
4.	Donald W. Schaffner, PhD	5D	439	**Excerpt Text:** 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.	No response needed.
4.	Donald W. Schaffner, PhD	5A	463	**Excerpt Text:** 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.	Text edited in the introduction to Section 4 to address this comment

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
4.1.	Darrell W. Donahue, PhD	5A	77	**Excerpt Text:** 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. - P. 62, lines 1-5 – need to provide some references here where the reader can go to find examples of outbreak data being used. - P. 63, lines 38-~44 – it is useful to mention that thresholds, if they do exist, are likely host-dependent as well.	A graphic was not added, but a pointer to the section containing the mathematical details was added. - Pg. 62 - Citations added - Pg 63 - Not added since those lines are taken directly from the NRC report. We do not have a citation to support the suggestion.
4.1.1.	Mark W. LeChevallier, PhD	5D	270	**Excerpt Text:** 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.	Text edited to address comments.
4.1.1.	Donald W. Schaffner, PhD	5A	464	**Excerpt Text:** 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.	Text edited for clarity
4.1.2.	Tony Cox, Jr., PhD	5A	32	**Excerpt Text:** 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.	Title to section 4.1.2 changed. Citation added to justify this perspective.
4.1.2.	Mark W. LeChevallier, PhD	5D	271	**Excerpt Text:** Page 67, line 44. Watch terminology. Infection is not the same as colonization. Revise this sentence.	No change made. Prior sentence provides context for this use.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
4.1.2.	Christine L. Moe, PhD	5A	339	**Excerpt Text:** 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.) **Image 339 shown below**	Text edited to include the citation for this phenomenon
4.1.3.	Darrell W. Donahue, PhD	5A	78	**Excerpt Text:** 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. P. 69, lines 40-45 – should make the point that in outbreak data there is often no known "dose" level.	4.1.3.: Not adopted. Style format is to only numbered to 3 levels -Pg 69: Text added to address this point
4.1.3.	Mark W. LeChevallier, PhD	5D	272	**Excerpt Text:** 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.	P. 68, line 2: Text edited to address comments. -P. 68, line 34: Text edited to address comments. P. 70, line 8: Text edited to address comments.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
4.1.3.	Christine L. Moe, PhD	5A	340	**Excerpt Text:** 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.	Text edited in Section 4.1.3 to address this comment Text edited in Section 4.1.3 to address this comment
4.1.3.	Christine L. Moe, PhD	5A	341	**Excerpt Text:** On page 68, lines 10-12, please provide the reference for the Salmonella dose-response relationship for illness.	Citation added
4.1.3.	Christine L. Moe, PhD	5C	349	**Excerpt Text:** 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.	No response needed.
4.1.3.	Christine L. Moe, PhD	5D	353	**Excerpt Text:** 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.	Text edited in Section 4.1.3 to address this comment

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
4.1.3.	Donald W. Schaffner, PhD	5A	465	**Excerpt Text:** 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.	Text added to section 6.2 to address comment No response necessary
4.1.4.	Christine L. Moe, PhD	5A	342	**Excerpt Text:** Page 70, section 4.1.4: It would be helpful to introduce and explain the concept of the Basic Reproductive Number (R0) as a measure of infectivity and modeling the spread of the disease in the population. R0 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).	A paragraph on R0 was added to section 4.1.4.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
4.1.4.	Christine L. Moe, PhD	5A	343	**Excerpt Text:** 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?).	Text edited in Section 4.1.3 to reflect comment
4.1.4.	Christine L. Moe, PhD	5A	344	**Excerpt Text:** 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.	Citation added to illustrate this point
4.1.4.	Donald W. Schaffner, PhD	5A	466	**Excerpt Text:** 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.	Additional text was added in Section 4.1.4 and a pointer to section 6.5.2 was added.
4.1.5.	Darrell W. Donahue, PhD	5A	79	**Excerpt Text:** Section 4.1.5 – fix obvious formatting errors. P. 72 – line 6 – add: "..rationale for the model and logic for its selection.." P. 74-75, Table 4.1 is a great addition to this text!	Section 4.1.5.: no obvious errors in this version exist - P. 72: Corrected as suggested -P. 74-75: No response needed.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
4.1.5.	Donald W. Schaffner, PhD	5A	467	**Excerpt Text:** 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?	Redundant text in 4.1.5.(b) was deleted for clarity. However, examples were not provided in this case to facilitate parallel structure with other points in Section 4.1.5
4.2.	Darrell W. Donahue, PhD	5C	87	**Excerpt Text:** 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.	Text has been added to section 4.2.1 to address this comments
4.2.	Joseph N.S. Eisenberg, PhD	5D	156	**Excerpt Text:** 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.	The edited version now reflects this structure.
4.2.	Donald W. Schaffner, PhD	5B	437	**Excerpt Text:** 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?	-Cassin and Powell added as footnotes since those are based on surrogate pathogens, they were explicitly included in the Table. -FAO/WHO added -No dose response available specifically for human exposure to *Listeria monocytogenes*

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
4.2.1.	Tony Cox, Jr., PhD	5C	33	**Excerpt Text:** 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.	Text edited in section 5.2.4 to address this point.
4.2.1.	Darrell W. Donahue, PhD	5A	80	**Excerpt Text:** P. 74-75, Table 4.1 is a great addition to this text! P. 76-77, chap number as well as eq…example, line 5 should state: "..(Equation 4.1)." and so on.	p. 74-75: No response needed. P. 76-77: Corrected in this version

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
4.2.1.	Darrell W. Donahue, PhD	5A	84	**Excerpt Text:** 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. **Excerpt References:** Donahue, D. W. 2005. Neural Networks: A Microbial Risk Assessment Tool. Presentation at the Society for Risk Analysis, 4-7 December, Orlando, FL. 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. Fausett, Laurene. 1994. Fundamentals of Neural Networks: Architectures, Algorithms and Applications. Prentice-Hall, Inc., New Jersey.	4.2.1: Text edited to include NN models and suggested citations added
4.2.1.	Joseph N.S. Eisenberg, PhD	5D	154	**Excerpt Text:** 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.	No edits made. The audience for this guideline, and this section in particular is risk assessors. The risk assessors that would typically be responsible for implementing exposure modeling would have sufficient statistics background.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
4.2.1.	Christine L. Moe, PhD	5A	345	**Excerpt Text:** 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.	Where practical an additional illustration was added (see chapter 1).
4.2.1.	Christine L. Moe, PhD	5A	346	**Excerpt Text:** 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.	Text edited as suggested Incubation period is addressed in Section 5.2.7 within the QMRA context of dynamic models. We are unaware of specific data to support including this comment into the document.
4.2.1.	Christine L. Moe, PhD	5B	348	**Excerpt Text:** 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.	That information is available in each of the primary citations provided in Table 4.1.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
4.2.1.	Donald W. Schaffner, PhD	5B	468	**Excerpt Text:** Page 82: Content: "E. coli O157:H7" Comment: Cassin et al. too Page 83: Content: "Salmonella" Comment: FAO/WHO too?	Footnote added to Table 4.1 to address comment Added to Table 4.1
4.2.1.	Donald W. Schaffner, PhD	5A	469	**Excerpt Text:** 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.	Text is correct as written because the beta poisson is also in that family of models (jin the exact form) Reference pointer added to refer readers to Section 5.5
4.2.3.	Darrell W. Donahue, PhD	5A	81	**Excerpt Text:** 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.	Edited as suggested.
4.2.3.	Christine L. Moe, PhD	5A	347	**Excerpt Text:** Page 80, line 31 – How does this Guidance manual define “valid dose-response data set”?	Text edited for clarity
4.2.3.	Christine L. Moe, PhD	5D	354	**Excerpt Text:** 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.	Where practical an additional illustration was added (see chapter 1). The Englehardt and Swartout 2004 reference is cited in the document.
4.2.4.	Tony Cox, Jr., PhD	5D	34	**Excerpt Text:** 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.	The text was edit to include the potential need to address subpopulation differences and host susceptibility issues

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
4.2.4.	Darrell W. Donahue, PhD	5A	82	**Excerpt Text:** 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).	General introductory text was added to the top of section 4.2.4 and 4.2.5 to address this comment. Sections on uncertainty and variability were not merged so that the structure would be parallel with the presentation in Chapter 5.
4.2.4.	Joseph N.S. Eisenberg, PhD	5D	155	**Excerpt Text:** 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.	Clarification added to make this paragraph more accessible and clear.
4.2.4.	Mark W. LeChevallier, PhD	5D	273	**Excerpt Text:** Section 4.2.4. See the discussion of uncertainty and variability above.	See responses above. No additional response needed.
4.2.5.	Joseph N.S. Eisenberg, PhD	5D	157	**Excerpt Text:** 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.	Edited as suggested.
4.2.7.	Mark W. LeChevallier, PhD	5D	274	**Excerpt Text:** 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.	No response needed.
4.2.7.	Christine L. Moe, PhD	5D	355	**Excerpt Text:** Pg 85, line 1 – please explain "receptor populations"	Edited for clarity

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
4.2.7.	Donald W. Schaffner, PhD	5C	438	**Excerpt Text:** 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.	Recommended citation added in section 4.1.3.
4.2.8.	Darrell W. Donahue, PhD	5A	83	**Excerpt Text:** 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. P. 85, there should be a short 1-2 paragraph section of conclusion to this chapter.	Text edited to address comment. Refer to next response also -P. 85: This subsection has been edited so that it serves as a forward-looking conclusion to the chapter.
5.	Tony Cox, Jr., PhD	6C	36	**Excerpt Text:** 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).	This comment presents an important limitation of MRA, but suggesting solutions is beyond the scope of the document.
5.	Darrell W. Donahue, PhD	6A	88	**Excerpt Text:** There is appropriate coverage for the information on Exposure Assessment. Some edits/suggestions are provided to improve clarity. Edits/suggestions: - 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.	-P. 89: Text added as suggested.
5.	Darrell W. Donahue, PhD	6B	106	**Excerpt Text:** 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.	No response needed.
5.	Joseph N.S. Eisenberg, PhD	6A	158	**Excerpt Text:** For the most part this chapter is well written and well organized.	No response needed.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
5.	Jeffrey K. Griffiths, MD, MPH	6A	230	**Excerpt Text:** 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].	No response needed.
5.	Jeffrey K. Griffiths, MD, MPH	6B	233	**Excerpt Text:** 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.	Text has been edited in section 5.2.8 to indicate that a more detailed treatment of infectious disease modeling may be discussed in a future volume of this guideline in section 5.2.7.
5.	Jeffrey K. Griffiths, MD, MPH	6B	234	**Excerpt Text:** 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.	Seasonality as an issue was added to the text in section 5.2.1.
5.	Jeffrey K. Griffiths, MD, MPH	6C	235	**Excerpt Text:** See above comment on seasonality and temporality above, as they contribute to variability (and sometimes uncertainty).	Addressed in previous comments; no additional response needed.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
5.	Mark W. LeChevallier, PhD	6A	275	**Excerpt Text:** 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.	Comment noted but no changes made.
5.	Mark W. LeChevallier, PhD	6B	276	**Excerpt Text:** 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.	Transport modeling including the use of hydraulic models was added to the text in section 5.2.2.
5.	Patricia L. Meinhardt, MD, MPH	6A	311	**Excerpt Text:** 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.	No response needed.
5.	Patricia L. Meinhardt, MD, MPH	6B	312	**Excerpt Text:** As an occupational and environmental medicine physician, addressing this question is outside of my area of expertise and I offer no response.	No response needed.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
5.	Christine L. Moe, PhD	6B	371	**Excerpt Text:** 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	This is an excellent observation and point. However, designing a monitoring program is beyond the scope of this guidance document. -Biomarkers: Text has been added (section 5.2.7) to indicate that topic may be addressed in a future volume of this guideline
5.	Gary S. Sayler, PhD	6A	413	**Excerpt Text:** 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.	5.1.12: Text edited for clarity as suggested. 5.2.1: The title of this section was edited to reflect this suggestion. 5.2.6: Sentence was deleted.
5.	Gary S. Sayler, PhD	6C	414	**Excerpt Text:** 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.	No additional response required.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
5.	Donald W. Schaffner, PhD	6A	440	**Excerpt Text:** 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.	Comment noted but no changes made.
5.	Donald W. Schaffner, PhD	6B	441	**Excerpt Text:** I think the chapter has a fairly comprehensive list already. I have suggested some references in detailed comments below.	No response needed.
5.	Donald W. Schaffner, PhD	6C	442	**Excerpt Text:** Coverage is sufficient.	No response required.
5.	Donald W. Schaffner, PhD	6A	470	**Excerpt Text:** 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.	Edited to include suggested citation Edited as suggested
5.1.	Joseph N.S. Eisenberg, PhD	6C	164	**Excerpt Text:** 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.	Sentence deleted.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
5.1.	Patricia L. Meinhardt, MD, MPH	6C	313	**Excerpt Text:** 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.	No response required.
5.1.2.	Christine L. Moe, PhD	6A	357	**Excerpt Text:** 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.	Text edited in Section 5.1.2 to explain this point
5.1.3.	Christine L. Moe, PhD	6A	358	**Excerpt Text:** Pg 90, lines 11-19 – please include exposure via hand-to-hand contact.	Edited as suggested
5.1.3.	Donald W. Schaffner, PhD	6A	471	**Excerpt Text:** 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?	Text edited for clarity Edited as suggested No edits made, clearer as list than sentence

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
5.1.4.	Christine L. Moe, PhD	6A	359	**Excerpt Text:** 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"	Edited for clarity Edited as suggested
5.1.5.	Christine L. Moe, PhD	6A	360	**Excerpt Text:** 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.	Edited as suggested
5.1.6.	Mark W. LeChevallier, PhD	6C	277	**Excerpt Text:** 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.	Addressed as described above.
5.1.7.	Darrell W. Donahue, PhD	6A	89	**Excerpt Text:** P. 92, lines 21-28 – should "sub-strain variability" be added to this listing?	-P. 92: No change made. Strain variability impacts would be reflected in the dose response component.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
5.1.8.	Tony Cox, Jr., PhD	6C	37	**Excerpt Text:** 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.)	This comment presents an important limitation of MRA, but suggesting solutions is beyond the scope of the document. However a discussion on uncertainty and variability was added to chapter 1.
5.1.9.	Darrell W. Donahue, PhD	6A	90	**Excerpt Text:** P. 93, lines 38-43 – can re-introduce the use of compartmental modeling/analysis in this section	Text edited as suggested.
5.1.9.	Mark W. LeChevallier, PhD	6C	278	**Excerpt Text:** Page 93, line 35. Suggest using “frequency” instead of “rates”.	Edited as suggested.
5.1.10.	Darrell W. Donahue, PhD	6A	91	**Excerpt Text:** P. 94, lines 28-32 – should address transparency here.	Text edited as suggested.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
5.1.11.	Darrell W. Donahue, PhD	6A	92	**Excerpt Text:** 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. P. 95, - lines 26-28 – need reference. P. 95, line 33 – Kelton is the correct reference.	- P. 94: Edits is section 5.10 address this comment. - P. 95, line 26: Reference added as suggested. -P. 95, line 33: Corrected.
5.1.11.	Donald W. Schaffner, PhD	6A	472	**Excerpt Text:** 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?	Citation added as suggested
5.1.12.	Darrell W. Donahue, PhD	6A	93	**Excerpt Text:** P. 96, lines 22-25 – need to refer the reader back to ch 2 to make the planning and scoping connection.	Edited as suggested.
5.1.12.	Christine L. Moe, PhD	6A	361	**Excerpt Text:** 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"	Edited as suggested Edited for clarity
5.1.13.	Darrell W. Donahue, PhD	6A	94	**Excerpt Text:** P. 99 – lines 7-8 – need to reiterate the idea of transparency in the last sentence. P. 99 – line 41 – include the word "..Exposure Assessment" (not "risk").	Edited both comments as suggested.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
5.1.13.	Christine L. Moe, PhD	6A	362	**Excerpt Text:** Pg 98, line 24 – it would be helpful to include an example scenario	Examples and case studies were not added for two reasons. First, the workgroup found during development of the document that selection of case studies was very difficult and second, at this stage in development of the document, any new examples would not have been peer reviewed.
5.1.13.	Donald W. Schaffner, PhD	6A	473	**Excerpt Text:** 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?	Edited for clarity Edited for clarity.
5.2.1.	Joseph N.S. Eisenberg, PhD	6A	159	**Excerpt Text:** 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.	The title of the section was edited as suggested by another reviewer. This change addresses the confusion noted in this comment.
5.2.2.	Darrell W. Donahue, PhD	6A	95	**Excerpt Text:** 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.	Text was edited to clarify this point and emphasize the illustrative examples.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
5.2.2.	Joseph N.S. Eisenberg, PhD	6B	161	**Excerpt Text:** 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. **Excerpt References:** 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.	Added section 5.1.3 How are Fate and Transport Considered in Exposure Assessment? Additional examples were not added.
5.2.2.	Mark W. LeChevallier , PhD	6C	279	**Excerpt Text:** Page 103, line 28. It is suggested that the explanation of exposure routes be placed into a footnote in Table 5.2.	Edited as suggested.
5.2.2.	Christine L. Moe, PhD	6A	363	**Excerpt Text:** 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.	Where practical an additional illustration was added (see chapter 1). The workgroup believes that the edits suggests for section 5.2.2 are not necessary.
5.2.2.	Christine L. Moe, PhD	6B	372	**Excerpt Text:** 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.	Edited as suggested, except human or animal not added because “natural or anthropogenic” is more explicit.
5.2.2.	Donald W. Schaffner, PhD	6A	474	**Excerpt Text:** Page 109: Content: "(simple as possible, but not simpler)." Comment: Cite Einstein.	Not referenced as this is common mathematical terminology
5.2.3.	Darrell W. Donahue, PhD	6A	96	**Excerpt Text:** 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.	Text edited to address this point.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
5.2.3.	Jeffrey K. Griffiths, MD, MPH	6A	231	**Excerpt Text:** 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.	Text edited as suggested.
5.2.3.	Christine L. Moe, PhD	6B	373	**Excerpt Text:** 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.	Text edited as suggested Text edited as suggested
5.2.3.	Donald W. Schaffner, PhD	6A	475	**Excerpt Text:** 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?	Not edited. List is easier to read in this case.
5.2.4.	Darrell W. Donahue, PhD	6A	97	**Excerpt Text:** 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. P. 108, lines 1-2 – input-output flow is also more broadly called the “mass balance” approach.	P. 107: No response needed. The guideline is written for risk assessors who understand simple dose response relationships. P. 108: Text edited as suggested.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
5.2.4.	Christine L. Moe, PhD	6B	374	**Excerpt Text:** 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.	Edited as suggested Where practical an additional illustration was added (see chapter 1).
5.2.4.	Donald W. Schaffner, PhD	6A	476	**Excerpt Text:** 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.). **Excerpt References:** 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.	Section 5.2.4 has been expanded and now includes references. Suggested references added.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
5.2.5.	Darrell W. Donahue, PhD	6A	98	**Excerpt Text:** P. 109, line 16 – insert "..between process steps.." P 109, lines 24-25 – need to add a caution about assuring transparency when converting conceptual relationships to mathematical relationships. P. 110, lines 5-15 – this example is not complete in its description. P. 110, lines 29 – p. 111, line 4 – need to move this section AFTER p. 111, line 24 for better clarity. P 110-116 – there are several issues with equation formatting that need to be addressed.	-P. 109: Edited as suggested -P. 110: All comments edited as suggested.
5.2.5.	Mark W. LeChevallier, PhD	-	280	**Excerpt Text:** 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?	P. 110: Edited for clarity. P. 114: Edited for clarity.
5.2.5.	Christine L. Moe, PhD	6A	356	**Excerpt Text:** 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.	Comment noted, but no changes made.
5.2.5.	Christine L. Moe, PhD	6A	364	**Excerpt Text:** 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.	Edited as suggested and simplified Not included to reduce redundancy. Variables are defined in text near the call –out to the Table.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
5.2.5.	Christine L. Moe, PhD	6B	375	**Excerpt Text:** Pg 109, section 5.2.5 – this section may belong on pg 96 with section 5.1.12	By leaving as a stand alone section, scenario analysis is highlighted as an important step rather than just as one component of the exposure assessment
5.2.6.	Christine L. Moe, PhD	6A	365	**Excerpt Text:** Pg. 115, line 3 – There is a typo where Nt and N0 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.	fixed Text edited to include suggested examples.
5.2.6.	Christine L. Moe, PhD	6A	366	**Excerpt Text:** 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.	Text moved to the first paragraph in section 5.2.6 to better introduce subsequent text. Text edited to include suggested text

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
5.2.6.	Donald W. Schaffner, PhD	6B	477	**Excerpt Text:** 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. **Excerpt References:** 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.	Suggested citation added
5.2.7.	Darrell W. Donahue, PhD	6A	99	**Excerpt Text:** P. 117, section 5.2.7 – this section is of lesser importance to the overall chapter.	No response needed.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
5.2.7.	Joseph N.S. Eisenberg, PhD	6B	162	**Excerpt Text:** 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. **Excerpt References:** 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.	References added as suggested.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
5.2.7.	Joseph N.S. Eisenberg, PhD	6B	163	**Excerpt Text:** 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. **Excerpt References:** 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.	References added as suggested. Riley et al kept as it refers to the SARS statement in the text.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
5.2.7.	Jeffrey K. Griffiths, MD, MPH	6B	232	**Excerpt Text:** 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.	A pointer to Figure 6.2 has been added in Section 5.2.7
5.2.7.	Christine L. Moe, PhD	6A	367	**Excerpt Text:** 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.	No changes made. In an effort to make each Chapter functionally stand-alone, the replication of this material was needed. The additional category suggested is in the text as the “Carrier” state, the text has been moved to make this more clear.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
5.2.7.	Donald W. Schaffner, PhD	6A	478	**Excerpt Text:** 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?	A reference has been added which helps to answer this question.
5.2.8.	Tony Cox, Jr., PhD	6C	35	**Excerpt Text:** 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.	No response needed. The text is intentionally non-prescriptive so that Agencies can adopt methods and approaches as needed and appropriate.
5.2.8.	Darrell W. Donahue, PhD	6A	100	**Excerpt Text:** P. 118 line 16 – insert "..determined in the planning and scoping phase before.." (this makes the connection back to chap 2 here).	Text added as suggested.
5.2.8.	Joseph N.S. Eisenberg, PhD	6A	160	**Excerpt Text:** 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.	Text edited as suggested.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
5.2.8.	Christine L. Moe, PhD	6A	368	**Excerpt Text:** 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.	Text was edited to indicate that more detail is provided in the subsequent sections. The title now follows from the previous section - refer to response above. A footnote was added to indicate that the term prevalence has a different meaning within the filed of epidemiology
5.2.8.	Christine L. Moe, PhD	6A	369	**Excerpt Text:** 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.	Text in question was deleted. Refer to response above. This section follows from text above (previously on p. 188 L26-28).
5.2.8.	Donald W. Schaffner, PhD	6A	479	**Excerpt Text:** Page 126: Content: "(WHO/FAO, 2008)." Comment: Citation is FAO/WHO, 2008	Edited as suggested
5.2.9.	Darrell W. Donahue, PhD	6A	101	**Excerpt Text:** P. 121, lines 16-23 – need to address transparency here too. P. 121-122 – need some examples provided right after p. 122, line 6 and in section 5.3.1 after line 32.	-P. 121: Text edited as suggested. -P. 121-122: No change made.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
5.3.	Joseph N.S. Eisenberg, PhD	6C	165	**Excerpt Text:** 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. **Excerpt References:** 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.	RSA added in section 5.3.3 text along with brief summary of approach.
5.3.3.	Darrell W. Donahue, PhD	6A	104	**Excerpt Text:** P. 124 lines 4-15 – need to reference this approach. Also, should these equation terms/variables be defined?	The work group did not feel this was necessary.
5.3.3.	Christine L. Moe, PhD	6C	376	**Excerpt Text:** 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.	No changes made, this specific point is made in the first paragraph of section 5.3.4

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
5.3.4.	Darrell W. Donahue, PhD	6A	103	**Excerpt Text:** P. 125 lines 9-15 – need to relate back to planning and scoping. P. 126 line 11 – need reference for Akaike criterion (An Information Criterion). P. 126 line 26 – modify as "A design of experiments technique called factorial design.." (reference: Design and Analysis of Experiments, D. Montgomery 2009). P. 128 lines 8-12 – need to address the use of showing the baseline scenario as a reference point for any sensitivity analysis.	P. 125: Text edited as suggested. -P.126: citation added -P. 126, line 26: edited as suggested -P. 128: edited as suggested
5.4.	Patricia L. Meinhardt, MD, MPH	6C	314	**Excerpt Text:** 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.	This concept is introduced in Section 6.4.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
5.4.	Christine L. Moe, PhD	6A	370	**Excerpt Text:** 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).	Examples and case studies were not added for two reasons. First, the workgroup found during development of the document that selection of case studies was very difficult and second, at this stage in development of the document, any new examples would not have been peer reviewed. However, an example of a conceptual mode was added to chapter 2.
5.4.	Christine L. Moe, PhD	6C	377	**Excerpt Text:** Pg 128, lines 8-12 – Please show examples of the "results of sensitivity and uncertainty analyses in tabular or graphical formats".	Where practical an additional illustration was added (see chapter 1).
5.5.	Darrell W. Donahue, PhD	6A	105	**Excerpt Text:** P. 129 – NOTE: there is a conclusion/summary to this chapter which is appropriate.	No response needed.
6.	Darrell W. Donahue, PhD	7A	108	**Excerpt Text:** 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. Edits/suggestions - P. 131 line 10 – need to address transparency here.	P. 131: Edited as suggested.
6.	Darrell W. Donahue, PhD	7B	116	**Excerpt Text:** 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. **Excerpt References:** -	NRC citation added at the bottom of Section 6.1. Codex Procedural manual was not added. Codex 1999 risk assessment framework was added instead.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
6.	Darrell W. Donahue, PhD	7C	117	**Excerpt Text:** Response: The detail level is appropriate for the purpose of this document.	No response needed.
6.	Joseph N.S. Eisenberg, PhD	7A	166	**Excerpt Text:** The detail presented in this chapter is sufficient. I just have a few suggestions that will enhance the utility of this chapter.	No response needed.
6.	Joseph N.S. Eisenberg, PhD	7C	174	**Excerpt Text:** I think that in general it does a good job in synthesizing chapters 3-5.	No response needed.
6.	Jeffrey K. Griffiths, MD, MPH	7A	236	**Excerpt Text:** 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.	Pointing out specific shortcomings of previous risk assessments is beyond the scope of this document.
6.	Jeffrey K. Griffiths, MD, MPH	7B	239	**Excerpt Text:** In the introduction (page 130) good risk characterization materials from the WHO/FAO should also be cited.	Added as suggested.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
6.	Mark W. LeChevallier, PhD	7A	281	**Excerpt Text:** 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.	Added to the intro paragraph to Chapter 6.
6.	Mark W. LeChevallier, PhD	7B	282	**Excerpt Text:** 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.	This is an interesting suggestion, but seems to be outside the scope of this document.
6.	Mark W. LeChevallier, PhD	7C	283	**Excerpt Text:** 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.	No changes made. All other reviewers indicate that adequate detail is provided.
6.	Patricia L. Meinhardt, MD, MPH	7A	315	**Excerpt Text:** 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.	No response needed.
6.	Patricia L. Meinhardt, MD, MPH	7B	316	**Excerpt Text:** I am unaware of any additional risk characterization guidance references that would be appropriate to add to this MRA Guideline.	No response needed.
6.	Gary S. Sayler, PhD	7A	415	**Excerpt Text:** No additional comment needed. Clear and appropriate.	No response needed.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
6.	Gary S. Sayler, PhD	7C	416	**Excerpt Text:** Generally well connected; to the point that pages 139-144 seem somewhat redundant.	No response needed.
6.	Donald W. Schaffner, PhD	7A	443	**Excerpt Text:** 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.	No response needed.
6.	Donald W. Schaffner, PhD	7B	444	**Excerpt Text:** See detailed comments for suggestions on other references to include.	No response needed.
6.	Donald W. Schaffner, PhD	7C	445	**Excerpt Text:** Detail is generally sufficient.	No response needed.
6.	Donald W. Schaffner, PhD	7B	480	**Excerpt Text:** 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.	Citation added as suggested
6.1.	Tony Cox, Jr., PhD	7C	38	**Excerpt Text:** 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.	Eq 6.1 was deleted as it was unnecessary.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
6.1.	Darrell W. Donahue, PhD	7A	109	**Excerpt Text:** 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 P. 132, line 5 – change "assessment" to "characterization" **Excerpt References:** -	Edited as suggested.
6.1.	Joseph N.S. Eisenberg, PhD	7A	167	**Excerpt Text:** 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.	Edits made to section 6.1 to address comments.
6.2.	Darrell W. Donahue, PhD	7A	110	**Excerpt Text:** P. 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	No changes made. Variability (G) and Uncertainty (H) are kept together in this list since they are discussed so closely in the document.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
6.2.	Jeffrey K. Griffiths, MD, MPH	7A	237	**Excerpt Text:** 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 point is well taken, but this section does not seem to be the appropriate place for it. As indicated we prefer to keep this pointing Chapters 4 and 5.
6.2.	Mark W. LeChevallier, PhD	7C	284	**Excerpt Text:** 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.	Safety factors are addressed in section 4.2.7 where it is indicated that because many pathogens are highly species-specific or produce different effects in different species, and immune response mechanisms can be highly variable across species, use of uncertainty, modifying or adjustment factors to justify extrapolation is highly suspect.
6.2.	Christine L. Moe, PhD	7A	378	**Excerpt Text:** 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.	No response necessary. Text edited as suggested.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
6.2.	Donald W. Schaffner, PhD	7A	481	**Excerpt Text:** 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.	Citation added as suggested Text edited as suggested
6.3.	Darrell W. Donahue, PhD	7A	111	**Excerpt Text:** P. 136, line 37 – include transparency discussion here. P. 137, line 41 – link ideas here back to planning and scoping.	Edited both comments as suggested.
6.4.	Darrell W. Donahue, PhD	7A	112	**Excerpt Text:** P. 138 lines 14-16 – move "Finally…" sentence down and combine with lines 39-40.	The sentence in question was deleted to address another reviewer's comment
6.4.	Joseph N.S. Eisenberg, PhD	7A	168	**Excerpt Text:** 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.	Edited for clarity.
6.5.	Joseph N.S. Eisenberg, PhD	7A	169	**Excerpt Text:** 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.	Edits were made to section 6.5 to address these comments.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
6.5.1.	Joseph N.S. Eisenberg, PhD	7A	170	**Excerpt Text:** 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.	Section 6.5.1 edited to address the main comments presented.
6.5.1.	Joseph N.S. Eisenberg, PhD	7A	171	**Excerpt Text:** 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.	Text edited for clarity and correctness as suggested

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
6.5.2.	Joseph N.S. Eisenberg, PhD	7A	172	**Excerpt Text:** 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.	Edited as suggested.
6.5.2.	Christine L. Moe, PhD	7A	379	**Excerpt Text:** 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.	Text was added to indicate that Figure 6.2 can be generalized to organisms with very short or no immunity by allowing the duration of incubation to approach zero. Typographical error corrected. Could be over or under- estimate. No change made. This is a very difficult question, the answer to which is provided to the extent possible in the text: "where stochastic events can have a major impact".
6.6.	Darrell W. Donahue, PhD	7A	113	**Excerpt Text:** 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. **Excerpt References:** -	DOX not added to table, as DOX is usually used prior to analysis, and the Table 6.1 is aimed specifically at sensitivity and uncertainty analysis.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
6.6.	Christine L. Moe, PhD	7A	380	**Excerpt Text:** 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.	No change made. Chapters are intended to stand-alone if needed, therefore the repetition on variability and uncertainty is intentional. Appropriate use should be based on a case-by-case basis. The workgroup believes it is beyond the scope of this document to add examples.
6.7.	Darrell W. Donahue, PhD	7A	114	**Excerpt Text:** p. 144. Section 6.7 – this section seems to be out of place here. Maybe place this section after section 6.8.	No change made since section 6.8 (as written) acts as a better closing to the Chapter.
6.7.	Jeffrey K. Griffiths, MD, MPH	7A	238	**Excerpt Text:** 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.	Edited as suggested to include discounting of future disease (classic economic approach) versus the avoidance of disease.
6.7.	Christine L. Moe, PhD	7A	381	**Excerpt Text:** 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.	Citations are provided describing the derivation of these metrics. Context for their use within Agencies is also provided in the text Section in question was moved to the bottom of section 6.3 (How do I prepare a risk characterization Typo corrected
6.8.	Tony Cox, Jr., PhD	7C	39	**Excerpt Text:** 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.	Edited for clarity.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
6.8.	Darrell W. Donahue, PhD	7A	115	**Excerpt Text:** 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. P. 147 – bottom – again an overall general conclusion paragraph would be useful here to pull risk characterization information together. **Excerpt References:** -	Text edited to include the suggested definitions. - No edits made to P. 147.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
6.8.	Joseph N.S. Eisenberg, PhD	7A	173	**Excerpt Text:** 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. **Excerpt References:** 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.	Validation is now defined explicitly. -P. 46 edited as suggested. -Citation added as suggested.
6.8.	Donald W. Schaffner, PhD	7A	482	**Excerpt Text:** 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.	Corrected as suggested Edited to address comment
7.	Darrell W. Donahue, PhD	8A	118	**Excerpt Text:** 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.	No response needed.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
7.	Joseph N.S. Eisenberg, PhD	8A	175	**Excerpt Text:** 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.	No response needed.
7.	Jeffrey K. Griffiths, MD, MPH	8A	241	**Excerpt Text:** 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.	Those levels would be under quantitative risk assessment. It is beyond the scope of this document to provide examples of successful risk management.
7.	Mark W. LeChevallier, PhD	8A	285	**Excerpt Text:** 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.	The discussion on how risk managers perform their jobs provides context for the risk assessor. Risk assessors need to know what types of decisions the risk managers are being asked to make.
7.	Patricia L. Meinhardt, MD, MPH	8A	317	**Excerpt Text:** 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.	No response needed.
7.	Gary S. Sayler, PhD	8A	417	**Excerpt Text:** Clear and well described. No additions needed.	No response needed.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
7.	Donald W. Schaffner, PhD	8A	446	**Excerpt Text:** 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.	No response needed.
7.	Donald W. Schaffner, PhD	8A	483	**Excerpt Text:** 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.	This context is relevant for the audience of this report.
7.1.	Joseph N.S. Eisenberg, PhD	8A	176	**Excerpt Text:** 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.	The presidential commission steps were moved to a text box. The workgroup believes the other references are also important to include as is.
7.1.	Christine L. Moe, PhD	8A	382	**Excerpt Text:** 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.	Readers can refer to the original document for commentary on the principles.
7.2.	Darrell W. Donahue, PhD	8A	119	**Excerpt Text:** P. 150, lines 15-27 – need to refer back to NRC 2009 reference and chap 2 (planning and scoping) to better focus this section. P. 151, lines 15 – p. 152, line 1-5 - this section really should be a separate section labeled “organization” or something similar.	NRC 2009 reference added. Planning and scoping reference added. The workgroup believes the section is appropriate as is.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
7.2.	Joseph N.S. Eisenberg, PhD	8A	177	**Excerpt Text:** 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.	This section details how risk assessors interface with risk managers, so is relevant for this chapter.
7.2.	Donald W. Schaffner, PhD	8A	484	**Excerpt Text:** 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. **Excerpt References:** 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.	Reference added.
7.4.	Tony Cox, Jr., PhD	8A	40	**Excerpt Text:** 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.	Text added – "Decision-analytic approaches which are recommended by the NRC evaluate the utility of specific policy options (NRC, 2009)." Acceptable risk discussion has been clarified as provided for historical perspective.
7.4.	Joseph N.S. Eisenberg, PhD	8A	178	**Excerpt Text:** 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.	Acceptable risk discussion has been clarified as provided for historical perspective.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
7.4.	Jeffrey K. Griffiths, MD, MPH	8A	242	**Excerpt Text:** 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.	The sentence stands out quite well where it is and is appropriate in section 7.4.
7.4.	Christine L. Moe, PhD	8A	383	**Excerpt Text:** 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.	It is beyond the scope of this document to provide pros and cons of risk management approaches.
7.4.	Donald W. Schaffner, PhD	8A	485	**Excerpt Text:** 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?	It is beyond the scope of the document to speculate why.
7.5.	Darrell W. Donahue, PhD	8A	120	**Excerpt Text:** 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	Table re-ordered.
7.5.	Donald W. Schaffner, PhD	8A	486	**Excerpt Text:** Page 163: Content: "(e.g., low- acid canning regulations)" Comment: Give citation?	Text edited – "e.g., *Clostridium botulinum* in low-acid canning"

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
7.6.	Darrell W. Donahue, PhD	8A	121	**Excerpt Text:** P. 156 – bottom – again an overall general conclusion paragraph would be useful here to pull risk characterization information together.	A summary has been added.
8.	Darrell W. Donahue, PhD	9A	122	**Excerpt Text:** 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.	No response needed.
8.	Joseph N.S. Eisenberg, PhD	9A	179	**Excerpt Text:** 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.	No response needed.
8.	Mark W. LeChevallier, PhD	9A	286	**Excerpt Text:** 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.	Text added – "Identification and communication with stakeholders can start with the planning scoping process." Text edited – "Risk communication shouldn't have an absolute end; it can be an ongoing process, just as risk assessment is an iterative process."
8.	Patricia L. Meinhardt, MD, MPH	9A	318	**Excerpt Text:** 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.	No response needed.
8.	Donald W. Schaffner, PhD	9A	447	**Excerpt Text:** 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.	The workgroup believes that the risk assessor should have the context for informing the public.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
8.	Donald W. Schaffner, PhD	9A	487	**Excerpt Text:** 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"	Reference added.
8.1.	Tony Cox, Jr., PhD	9A	41	**Excerpt Text:** 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.	Text added – "At its best risk communication results in informative and productive exchanges and can be joint problem-solving by legitimate stakeholders and the government."
8.1.	Donald W. Schaffner, PhD	9A	488	**Excerpt Text:** Page 165: Content: "Inform the public about risk" Comment: Really there are many publics: the general public and many different stakeholders.	The many aspects of "public" are covered in section 8.3.
8.2.	Darrell W. Donahue, PhD	9A	123	**Excerpt Text:** P. 157, lines 43-44 – need to include transparent in this discussion.	These are OMB principles. It is beyond the scope of this document to suggest modifications to OMB principles.
8.2.	Donald W. Schaffner, PhD	9A	489	**Excerpt Text:** Page 165: Content: "and the public." Comment: Again, many publics...	The many aspects of "public" are covered in section 8.3.
8.3.	Donald W. Schaffner, PhD	9A	490	**Excerpt Text:** Page 166: Content: "all persons who produce and consume" Comment: It would also include people that handle ground beef (e.g., restaurants, supermarkets)	Edit made.
8.4.	Darrell W. Donahue, PhD	9A	124	**Excerpt Text:** P. 159. Lines 14-16 – include: addressing the need to develop for targeted (to the specific audience) communication materials.	Text added – "Communication materials targeted to many different specific audiences may be developed."

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
8.4.	Jeffrey K. Griffiths, MD, MPH	9A	243	**Excerpt Text:** 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.	Text added – "Communication materials targeted to many different specific audiences may be developed."
8.4.	Jeffrey K. Griffiths, MD, MPH	9A	244	**Excerpt Text:** 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.	Text added – "Communication materials targeted to many different specific audiences may be developed." Examples added.
8.8.	Darrell W. Donahue, PhD	9A	125	**Excerpt Text:** P. 161, lines 20-21 - need to include transparent in this discussion.	Text added – "Communication of this information is important for the transparency of the risk assessment."
8.9.	Donald W. Schaffner, PhD	9A	491	**Excerpt Text:** Page 169: Content: "—Salmonella." Comment: Italics	Italics added.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
8.10.	Donald W. Schaffner, PhD	9A	492	**Excerpt Text:** Page 170: Content: "How In-Depth Can I Communicate?" Comment: Awkward phrasing	This title was maintained.
8.12.	Tony Cox, Jr., PhD	9A	42	**Excerpt Text:** 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).	It is beyond the scope of this document to provide this level of detailed guidance.
8.12.	Darrell W. Donahue, PhD	9A	126	**Excerpt Text:** P. 163, line 3 – include: "..planning, skills and practice.."	Text edited – "Successful risk communication requires strategic planning, skills, and practice."
8.12.	Jeffrey K. Griffiths, MD, MPH	9A	245	**Excerpt Text:** 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.	Providing examples of failed risk communication attempts is beyond the scope of this document.
8.14.	Tony Cox, Jr., PhD	9A	43	**Excerpt Text:** 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.	The workgroup believes it is relevant for risk assessors to know that their agency may be involved in more general communication strategies.
8.14.	Darrell W. Donahue, PhD	9A	127	**Excerpt Text:** P. 165 – bottom - again an overall general conclusion paragraph would be useful here to pull risk characterization information together.	Summary was added.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
9.	Jeffrey K. Griffiths, MD, MPH	1B	185	**Excerpt Text:** 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.	HACCP was added to the glossary.
9.	Donald W. Schaffner, PhD	-	493	**Excerpt Text:** 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?	The descriptions are lengthy and it is beyond the scope of this project to summarize OMB's description. HI has been added to the glossary. ID50 has been added to definition. Text added to definition of uncertainty.
11.	Jeffrey K. Griffiths, MD, MPH	1B	187	**Excerpt Text:** 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.	Adding this information is beyond the limitations of the budget and timeline for this project.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
11.	Donald W. Schaffner, PhD	-	494	**Excerpt Text:** 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	Batz 2011 added.
11.	Donald W. Schaffner, PhD	-	495	**Excerpt Text:** 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.	Scallan references added. Changed to FAO/WHO

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A.	Jeffrey K. Griffiths, MD, MPH	1B	188	**Excerpt Text:** 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.	The workgroup believes the present format of appendix A is very clear.
A.	Christine L. Moe, PhD	1B	324	**Excerpt Text:** 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.	Text added – “Not all of these example assumptions will apply in all cases.” Apostrophes corrected.

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
B.	Jeffrey K. Griffiths, MD, MPH	1B	189	**Excerpt Text:** 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."	The table of contents should be enough to refer the reader to sections.
B.	Patricia L. Meinhardt, MD, MPH	1B	295	**Excerpt Text:** 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.	Footnote added – "Some questions concerning the host may be 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."

MRA Section	Reviewer	Charge Question	Comment Excerpt No.	Comment Excerpt, Notes, and References	Response
B.	Patricia L. Meinhardt, MD, MPH	1B	296	**Excerpt Text:** 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.	Text added as suggested.
B.	Christine L. Moe, PhD	1B	325	**Excerpt Text:** 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.	The questions in appendix B were revised.

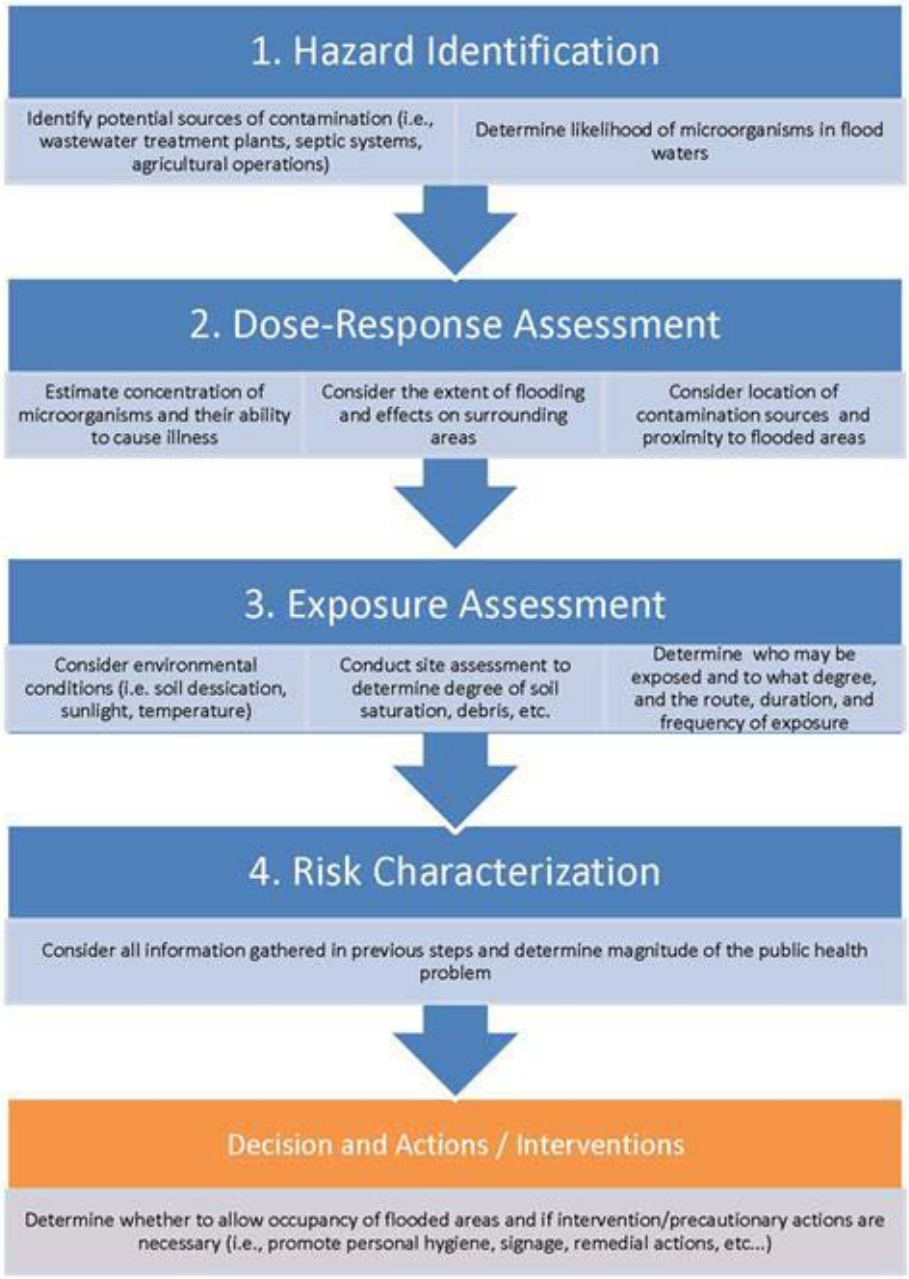
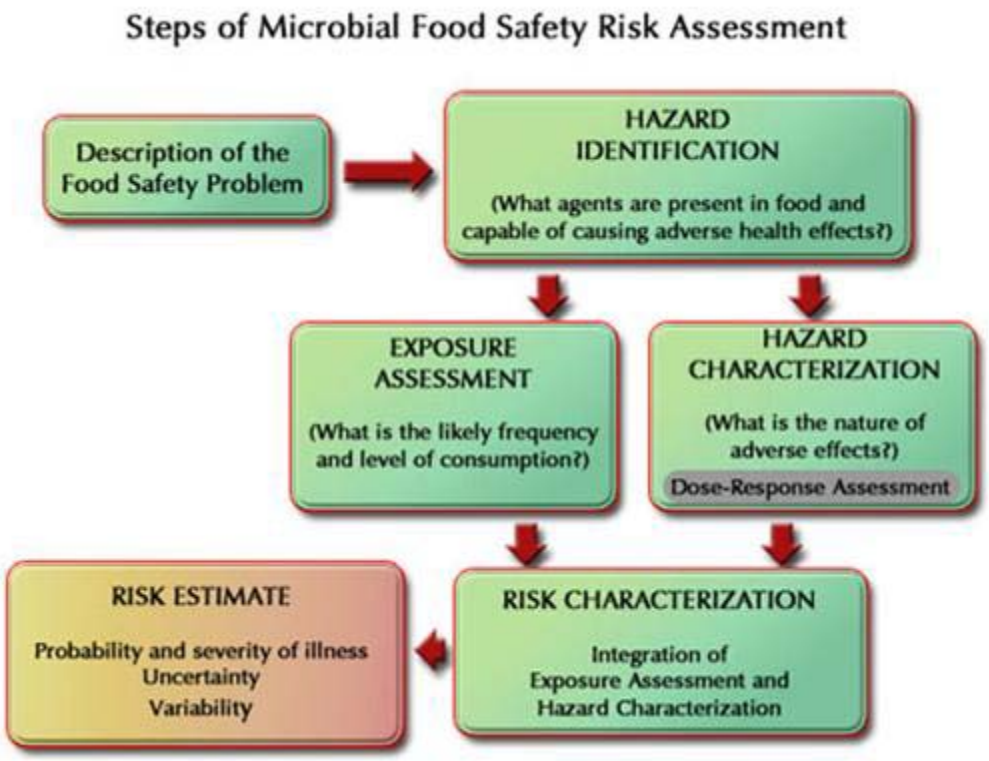


Image for Comment 384:

Image for Comment 328:



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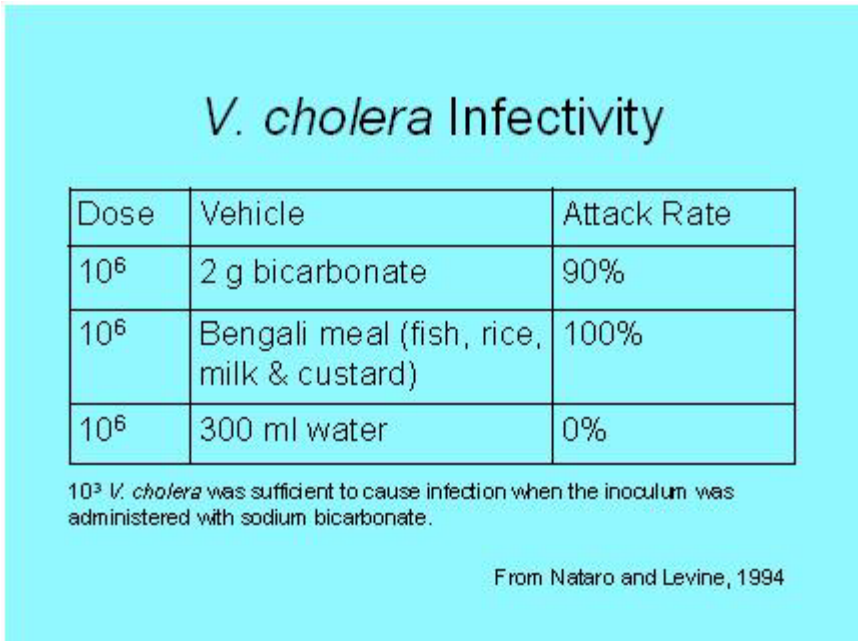

V. cholera Infectivity

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