

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460



OFFICE OF THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

June 18, 2010

EPA-SAB-10-008

The Honorable Lisa P. Jackson
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Subject: Review of EPA's Microbial Risk Assessment Protocol

Dear Administrator Jackson:

In response to a request from EPA's Office of Water (OW), the Science Advisory Board (SAB) convened the Drinking Water Committee to conduct a review of EPA's draft document, *Protocol for Microbial Risk Assessment to Support Human Health Risk Assessment for Water-Based Media*, henceforth referred to as "the MRA Protocol." The Office of Water (OW) has performed quantitative microbial risk assessments (MRAs) in support of new regulations for microbial pathogens in drinking water under the Safe Drinking Water Act (SDWA). MRAs (although not formal quantitative MRAs) have also partially supported the development of health-based ambient water quality criteria and biosolids criteria under the Clean Water Act (CWA). These criteria have assisted in protecting against potential adverse human health outcomes and exposures to infectious disease microorganisms in recreational waters and from land application of wastewater biosolids. OW developed "the MRA Protocol" to provide Agency guidance for performing microbial risk assessments. Current Agency risk assessment guidance is geared towards chemical risk assessment, but MRAs do not fit completely within the chemical-risk framework because of microbial and host factors that are specific to microbial risk assessments. The MRA Protocol was developed to help risk assessors address these factors in a consistent manner.

The SAB was asked to provide recommendations in several areas: how to improve the overall approach, the applicability of the protocol, the reasonableness of the protocol, the clarity of the protocol, the completeness and robustness of the protocol, and the ease of use of the protocol for conducting water-based microbial risk assessments.

The Committee commends the Agency for all the work undertaken and for taking a leadership role in the field of microbial risk assessment. This MRA document had been in development for many years and has undergone extensive internal and external review. It is important for EPA to complete this document as soon as possible as it will likely become an important document in this area. The key points and recommendations of the Committee are detailed in the report. Below is a brief summary.

Overall, the Committee finds the document to be comprehensive and inclusive of key information, but believes technical editing is needed to provide conciseness, clarity, and parallel structure between the chapters. The Committee also finds that the document does not fulfill its intended purpose as a “protocol.” A protocol generally implies a set of specific steps that would be undertaken to perform an MRA. This document does not provide those steps; rather, it serves as an excellent introduction to MRA by describing the conceptual framework, types of data and models, and the general process for undertaking an MRA.

The Committee strongly recommends the finalization and acceptance of this document, with appropriate modifications. The Committee recommends the following: (a) review and revision by a technical editor; (b) rename and restructure the document as an Introduction to MRA; (c) add more illustrative examples of actual EPA (or other) MRAs throughout the document with their strengths and weaknesses; (d) after publishing this document, develop a second, more advanced MRA document in the near future that would be a true protocol for conducting MRAs and/or a series of white papers that would address specific technical topics in greater detail. With such modifications, this document would represent a valuable foundation block in the field of MRA for the Agency.

Again, the SAB wants to express its overall admiration for the extensive work done by the Agency on this important topic of microbial risk. The SAB appreciates the opportunity to provide EPA with advice. We look forward to receiving the Agency’s response.

Sincerely,

/Signed/

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Chair
EPA Science Advisory Board

/Signed/

Dr. Joan B. Rose
Former Chair
Drinking Water Committee

/Signed/

Dr. Jeffrey Griffiths
Chair
Drinking Water Committee

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Drinking Water Committee for the Review of
EPA's Microbial Risk Assessment Protocol**

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ACRONYMS

CWA	Clean Water Act
DWC	Drinking Water Committee
EPA	Environmental Protection Agency
HACCP	Hazard Assessment and Critical Control Point
ILSI	International Life Sciences Institute
MRA	Microbial Risk Assessment
OST	EPA's Office of Water, Office of Science and Technology
OW	EPA Office of Water
SAB	Science Advisory Board
SDWA	Safe Drinking Water Act

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EXECUTIVE SUMMARY

EPA's Office of Water (OW) requested that the Science Advisory Board (SAB) Drinking Water Committee (DWC) review its draft *Protocol for Microbial Risk Assessment to Support Human Health Protection for Water-Based Media*, henceforth referred to as the "the MRA Protocol." There were five charge questions, which focused on an overview of the document and on the specific chapters of the document. These charge questions and responses are detailed in the report and the major recommendations from the Committee are highlighted below. The charge questions in their entirety are also presented in the Appendix of this report.

Overall, the Committee finds the document to be comprehensive and inclusive of key information, but believes technical editing is needed to provide conciseness, clarity, and parallel structure between the chapters. However, the Committee finds that the document does not fulfill its intended purpose as a "protocol." A protocol generally implies a set of specific steps that would be undertaken to perform, in this case, an MRA. This document does not provide those steps. However the Agency has done a tremendous amount of work on MRA and is commended for its leadership in this area, and this compilation serves as an excellent introduction to MRA by describing the conceptual framework, types of data and models, and the general process of performing an MRA. It is important that this document be finalized as soon as possible. The Committee recommends the following:

- Add more examples of actual EPA (or other) MRAs throughout the document, with a concise summary of their strengths and weaknesses;
- Rename and restructure the document as an Introduction to MRA rather than a Protocol;
- Develop a second, more advanced MRA document that would provide a step-by-step process for conducting MRAs in the near future and/or a series of white papers that would address specific technical topics in greater detail;
- Move the information from the appendices into the body of the text.
- Clearly specify the target audience and, if there is more than one audience, clearly specify how they might differ in using the document;
- Provide an index at the end of the document.

Planning & Scoping and Problem Formulation Chapter

The Committee finds that the Planning & Scoping and Problem Formulation chapter is generally useful. One recommendation the Committee has to improve this chapter is to:

- Include some additional clarification to indicate when stakeholders should be consulted in the process, and whether the result of a planning/scoping and problem formulation exercise would be subject to external review.

This chapter is also missing some information that would allow the reader to readily follow how the problem formulation is linked to the MRA process, and then to the desired end products. The linkage between the identified problem, and implementation of the MRA process

could be better outlined through the use of flow charts, figures, or logic trees. The Committee recommends:

- Formatting all the diagrams in the chapter to the standard logic-diagram format.

Exposure Chapter

The Exposure chapter provides a good, concise discussion of the key issues related to exposure assessment and the role of exposure assessment in the overall risk assessment; however some weaknesses and omissions were identified. Sensitivity analyses of MRAs have shown that the greatest source of variability in risk assessment is from defining the exposure. It is therefore vital to consider a comprehensive range of possible exposures to adequately describe possible MRAs. The exposure profile, the sum result of exposure characterization, is not given adequate treatment in this chapter and is not comprehensive enough. The chapter focuses on endemic exposures rather than episodic exposures, the latter which are more likely to result in higher concentrations of pathogens in treated water. The chapter also addresses risks from recreational exposure more than risks from drinking water exposure. Drinking water examples, however, should be used throughout, including unusual exposure routes associated with biofilms and inhalation. The subject of indicator organisms instead of direct measurements of pathogens is not discussed and should be added. Indicator organisms are used extensively in environmental risk management as indicators of disinfection efficacy and provide many of the temporal and spatial data sets on sources, transport and fate. Both the uncertainty associated with using indicator organisms and situations in which indicator organisms are more or less likely to be present than the true pathogens of concern should also be addressed in this chapter. The Committee recommends:

- Bolstering the discussion of the exposure profile;
- Adding a discussion of drinking water exposures and the complex issues associated with doing so, including water treatment barriers;
- Adding examples of MRAs used in drinking water exposure scenarios;
- Adding a discussion of exposures from the use of reclaimed wastewater, recycled water, and gray water;
- Adding a discussion of episodic exposures;
- Adding a discussion of using indicator organisms instead of direct measurements of pathogens in water.

Other suggestions for improving the chapter include:

- Emphasizing not only the similarities but also the differences that exist between chemical exposure assessment and microbial exposure assessment;
- Highlighting data needs for microbial exposure assessment, and how they differ from the data needs for chemical exposure assessment;
- If possible, giving specific suggestions about possible data sources, or how data might be obtained, for performing an MRA;
- Incorporating Appendix F, which is only one page in length, into this chapter; possibly as a “text box” if the authors think that it is disruptive to the overall flow.

- Adding examples of recently published MRAs used to guide beach closures and recreational exposures;
- Expanding the discussion regarding analytical methods and the interpretation of results with a section heading.

Human Health Effects Chapter

The Human Health Effects chapter is largely devoted to dose-response models. The Committee recommends separating this material into two chapters, one on dose-response and one on human health effects. The discussion on dose-response models was fairly comprehensive and thorough, when combined with Appendix G. The material from Appendix G should be brought into the text, but it should be rewritten by an expert statistician. The Committee strongly recommends:

- Having an expert statistician rewrite the material in Appendix G for accuracy in its description of the extant literature and methods, and for appropriate continuity between the discussions of the various statistical techniques.

Currently many animal feeding studies do not meet the criteria for developing statistically best-fit dose-response models. However, animal data sets are available and have been assessed. Thus this chapter should include a discussion of animal models that would be useful for the future, for example, the gnotobiotic piglet. The Committee recommends:

- Adding a discussion of animal models that would be useful for the future, for example to address competency of the host to support infection and disease processes.

Description of the data sets used for the dose-response curve fitting and the variability around the parameters should be included, and can be used further in MRA during uncertainty analysis. This characterization of the data sets may allow the reader to better understand how the quality of the data set and how the uncertainties in the data set affect the confidence one has in the dose-response curve. These details should include information about the microbial and host factors, such as pathogen strain and virulence, and host age. The Committee recommends:

- Adding a discussion of uncertainty in dose-response modeling arising from data sets, low dose extrapolation, and microbial and host factors.

Responding to the two charge questions on mathematical modeling of health outcomes and animal or *in vitro* models could have been more vigorous had the health effects of interest been defined. A better description of the human health outcomes associated with exposure to the wide range of environmental pathogens should be included in a very specific chapter devoted to this topic. A major observation was that this chapter contained little discussion of the health effects of interest and how mathematical approaches could be used to incorporate these effects into probability models or disease transmission models; the human health outcomes were not defined or delineated in sufficient detail. The majority of the chapter focused on dose-response analysis, obviously an important topic, but did not define the health effects of interest *per se* to which modeling should be applied.

The Committee recommends the following:

- Making the dose-response section a separate chapter from the description of the health effects;
- Expanding the discussion of health effects to include defining and delineating health outcomes;
- Including a description of the major health syndromes and delineating the chronic and acute effects;
- Providing examples of the health effects of interest, and how they have been used in prior risk assessments;
- Adding specific health effects information in the compendium of mathematical models;
- Adding a discussion of the spectrum of severity of health effects that may occur in a population;
- Adding a discussion of the spectrum of syndromes caused by a single microbial agent;
- Moving, or concisely reiterating, some or all of the susceptible population subsection in Chapter 2, to this chapter;
- Adding a discussion of host response concepts such as timing or onset of infection and disease severity;
- Removing the discussion about quality of life as it is not part of the risk assessment process.

Risk Characterization Chapter

The clarity and utility of the Risk Characterization chapter could be improved in several ways by connecting this chapter to the previous ones. It would be helpful to have summaries at the ends of the Exposure chapter and Human Health Effects chapter about what pieces of information need to be brought forward from those respective chapters and folded into a risk characterization. Then, at the beginning of the Risk Characterization chapter, it would be helpful to summarize the elements that need to be drawn from the earlier chapters and incorporated into a risk characterization. This section should explicitly refer back to the Planning & Scoping and Problem Formulation chapter. The discussion of dose-response models from the Human Health Effects chapter for use in the Risk Characterization chapter is confusing, and it is not clear which framework and models should be used to reflect different aspects of the risk assessment. The uncertainty, variability, and sensitivity analysis section of this chapter is good and does not omit any significant approaches or methods. To improve the chapter, the Committee recommends:

- Adding summaries at the ends of Chapters 3 and 4 about what pieces of information need to be brought forward from those respective chapters and folded into a risk characterization;
- Summarizing the elements that need to be drawn from the earlier chapters and incorporated into a risk characterization at the beginning of Chapter 5;
- Trimming unnecessary detail and redundancy about the models in these chapters (perhaps, capturing the detail in a second more advanced MRA document and/or technical white papers);

- Clarifying explicitly the different roles that the (same or different) models play in each of these aspects of the risk assessment. These changes will ensure that the reader understands what needs to be accomplished by the modeling exercise in each step;
- Adding text to explicitly refer back to the problem formulation, planning and scoping described in Chapter 2, especially Sections 2.1 and 2.2;
- Placing some of the topics that are in Appendix D that are not already addressed in Chapter 5 (i.e., the topics covered in Sections D.4-D.10), in an overview/summary format within Chapter 5;
- Acknowledging, and describing in an appropriate level of detail, the principles and practices regarding uncertainty, variability and sensitivity analysis presented in existing Agency documents that are, or could be, relevant to the conduct of MRAs;
- Editing the chapter to better focus the chapter and to assure that the essential elements of the chapter are not lost in the tangential discussions and excessive detail. Some of the specific edits are detailed in the report.

INTRODUCTION

This report was prepared by the Science Advisory Board (SAB) Drinking Water Committee (DWC) (the “Committee”) in response to a request by the Agency’s Office of Water (OW) to review their draft document, *Protocol for Microbial Risk Assessment to Support Human Health Protection for Water-Based Media*, henceforth referred to as “the MRA Protocol.”

The Office of Water (OW) has performed microbial risk assessments (MRA) in support of new regulations for microbial pathogens in drinking water under the Safe Drinking Water Act (SDWA). Specifically, quantitative MRAs have been performed in developing the *Surface Water Treatment Rule* and the *Long-Term Enhanced Surface Water Treatment Rule*. MRAs (although not formal quantitative MRAs) have also partially supported the development of health-based ambient water quality criteria and biosolids criteria under the Clean Water Act (CWA). These criteria have assisted in protecting against potential adverse human health outcomes and exposures to infectious disease microorganisms in drinking waters, recreational waters and land application of wastewater biosolids. OW developed “the MRA Protocol” to provide the Agency with more specific guidance on performing microbial risk assessments. Current Agency risk assessment guidance is geared towards chemical risk assessment, but MRAs do not fit completely within the chemical-risk framework because of microbial and human host factors that are specific to infectious disease and microbial risk assessments. The MRA Protocol was developed to improve risk assessments by Agency scientists and to address approaches to data and models in a consistent manner.

General features of the MRA Protocol document include: 1) a modular component concept; 2) flexibility to allow for unique Agency requirements which could be inserted or used to replace a set of default parameters; 3) discussion of various risk assessment applications including for regulatory purposes, outbreak investigation, identification and prioritization of research, investigation of risk-risk trade-offs, emergency response, and mitigation; 4) consistency with the companion EPA document, the *Thesaurus of Terms Used in Microbial Risk Assessment*, and 5) development of appendices showing details on dose-response modeling applications, flow diagrams for various types of assessments, and general considerations for conducting MRAs.

The MRA Protocol document includes chapters on the following: 1) problem formulation, with planning, scoping, and tiered conceptual modeling; 2) exposure, which includes pathogen occurrence and exposure analysis; 3) human health effects, with dose-response and health effects, dose response modeling applications, and dynamic population susceptibility models; and 4) risk characterization, which applies EPA’s Risk Characterization Handbook, invoking uncertainty, variability, comparisons to similar risks, alternative approaches/solutions, and input to inform risk management decisions.

The SAB was asked to provide recommendations in the following areas: how to improve the overall approach, the applicability of the protocol, the reasonableness of the protocol, the clarity of the protocol, the completeness and robustness of the protocol, and the ease of use of the protocol for conducting water-based microbial risk assessments. This task was posed to the

Committee in the form of specific charge questions detailed in the report below and also in the Appendix of the report.

The Committee deliberated on the charge questions during a September 21-22, 2009 face-to-face meeting and discussed its draft report in a subsequent conference call on November 19, 2009. The Chartered SAB conducted a quality review of this document on March 24, 2010. Originally the charge question pertaining to Overarching Considerations was the last charge question, but the Committee believed that it was more appropriate as the first charge question, which is reflected below. The responses that follow represent the views of the Committee.

RESPONSE TO EPA CHARGE QUESTIONS

1. Charge Question 1 – Overarching Considerations

EPA's Office of Water, Office of Science and Technology (OST) would like this Protocol to provide a comprehensive and robust suite of approaches, tools, methods, and procedures to meet EPA's overall needs in preparing for, and conducting typical MRAs. OST would also like the Protocol to be informative, easy to use and understand, and useful to outside stakeholders (states, communities, utilities, industry, and impacted parties).

Please comment on the following:

- a) utility of the Protocol for meeting EPA's overall needs, particularly on the comprehensiveness and robustness of the Protocol;*
- b) flow and continuity within and between chapters;*
- c) ease of use and utility for outside stakeholders;*
- d) any changes or enhancements to the Protocol to ensure it meets the needs of EPA and outside stakeholders.*

1.1 Utility of the Protocol for Meeting EPA's Overall Needs, Particularly the Comprehensiveness and Robustness of the Protocol

The Committee believes that the MRA Protocol is a valuable document that should be finalized quickly. However, this document is not really a protocol; that is, it does not lay out a step-by-step procedure for performing a microbial risk assessment. Rather, this document is an informative overview of the MRA process, describing the components of an MRA and delineating the data needs and possible models that could be used.

The document is quite comprehensive in terms of addressing the topic of microbial risk assessment at an introductory level, and the Committee did not identify major information gaps. The chapters are well organized but additional editing is needed to improve the flow of information, particularly in the use of topic sentences to introduce forth-coming ideas and provide transition between paragraphs and sections. The document reads much like a textbook and, in this respect, it is helpful and convenient to have all information on MRA readily available in one location. This document is very useful and could be one of the main resources on MRAs in the future.

- To make the document more comprehensive and robust, EPA should add examples of MRAs conducted on microbial pathogens. These examples should include a concise description of the strengths or weaknesses of the MRA; the specific data gaps which were highlighted in the MRA; and when new analytical tools and methodologies were either used or identified as needed.

The chapters introduce the readers to the various components of MRAs, whereas the Appendices go into greater detail with figures, tables and frameworks in each area. The discussion on the roles of the risk assessors and the risk managers is good and clearly delineates these roles. Attempts should be made to condense the writing of the document, to make it more concise, without sacrificing the clarity in the document and should undergo technical editing.

This document should be quite useful to professionals inside and outside of the government who conduct MRAs, and to scientists who are new to the field of MRA and who want to learn about this process. A determination should be made to establish the intent of this document: is it a Framework, a Guidance document, or an Introduction to Microbial Risk Assessment? In its present form, the document is more of an introduction to Microbial Risk Assessment than a Protocol. The Committee recommends the following:

- Finalize this document as an Introduction to MRA;
- In the near future, develop a more advanced document on MRA.

One could then progress from an Introduction to MRA (this document) to advanced topics in MRA to actual MRAs on specific microbes; the actual protocol would be the second document and would lay out step by step procedures on how to conduct MRAs. The examples of prior MRAs, and the concise descriptions of the strengths and weaknesses, data gaps, methodological needs, and usefulness to policy and regulatory decisions will inform this progression and help focus subsequent documents.

1.2 Flow and Continuity Within and Between Chapters

The flow and continuity within all sections – the Executive Summary and Chapters 1-5 – are good but need to be improved. All of the chapters and the Executive Summary are well-written and informative. They are verbose in certain sections, however, and some condensation is warranted. The flow between the Problem Formulation, Exposure, Human Health Effects, and Risk Characterization chapters could be improved through the use of additional flow diagrams. Most of the Appendices are excellent, and add a wealth of detail to the document.

Collectively, the DWC thinks that the information from the appendices should be moved into the body of the text. The Committee recommends that the Agency quickly produce (with good editing) this current MRA document as an introduction to MRA, while keeping some of the advanced and detailed discussions for inclusion in a second, more advanced MRA document and/or set of technical white papers.

Suggestions from the DWC members that would improve the flow and while producing this as an overview of or introduction to MRA include:

- Placing Appendix A back into the text in the appropriate chapter;
- Making Appendix B a separate chapter in the front or close to the front of the document;
- Placing Appendix D toward the beginning of the document to illustrate general risk principles as a separate chapter;
- Placing Appendix E at the end of one of the chapters as a concluding section in that chapter;
- Placing Appendix F at the end of the appropriate chapter.
- Appendix G should be removed from the Appendix and placed into the document in the dose-response section but only after a senior technical analyst with statistical expertise review Appendix G in particular, for accuracy in its description of the extant literature and methods, and for appropriate continuity between the discussions of the various statistical techniques (see response to charge question 4).

1.3 Ease of Use and Utility for Outside Stakeholders

There was a good deal of discussion regarding the identities of the document's intended audience and the primary stakeholders. The DWC concluded that this document was meant to first serve the scientists within the Agency and the groups they work with who may take on MRAs, and that the secondary audience and stakeholders would be the water industry. This document should be useful for these outside stakeholders as a primer for the scientist who is new to the field and wishes to understand the EPA's MRA process. The stakeholders and scientists new to this area should be able to read the main chapters and understand them.

1.4 Changes or Enhancement to the Protocol to Ensure That it Meets the Needs of EPA and Outside Stakeholders

The intended primary purpose of this document was to inform and guide EPA staff and its contractors in conducting MRAs. An important secondary purpose was for the document to inform those outside the agency on how these EPA assessments are done. The document does a good job of describing the process thoroughly and helps a reader unfamiliar with the process to understand what an MRA might entail and the types of information needed. The Agency's goal of transparency is furthered by this type of document.

The strength of the document, explaining the principles of MRA, may also be its weakness **if the document was intended to be a protocol**. The emphasis of the current document appears to be more on understanding MRA than in implementing an MRA. This focus is apparent in comparing Chapters 2 and 4. Chapter 2 has a sense of direction and describes a process of implementation with specific step-by-step instructions on how to formulate a problem to be addressed by MRA, and how to develop a suitable conceptual model. In contrast, Chapter 4 is much more explanatory; the reader is not given directions, for example, on how to assess and choose dose-response models.

One idea for resolving this tradeoff of providing too much direction without enough explanation or vice versa, is to develop a step-by-step protocol subsequent to revising the current document (the current document being an Introduction to MRA). This first document will

provide the understanding, in which the steps in an eventual protocol can be linked to expanded explanations in this Introduction to MRA. Such a protocol could then follow the organization and format of other EPA protocols, such as Method 1623. It may help to create an overall visual schema, using a flow chart or decision tree, of the overall MRA process at the beginning of the document. This approach is used in an abbreviated fashion in Appendix D with Text boxes D.1, D.2, and D.3. It may further help to provide in the introduction a thorough description of actual well-developed MRAs as examples to guide the reader, such as the MRAs performed by EPA in support of the development of both the *Surface Water Treatment Rule* and the *Long-Term Enhanced Surface Water Treatment Rule*.

Other enhancements to the document include the following:

- Clearly specify the target audience and, if there is more than one audience, clearly specify how they might differ in using the document;
- Provide an index at the end of the document;
- Provide a better description of the Monte Carlo method and other appropriate probabilistic methods in the Risk Characterization chapter with appropriate reference (e.g., The Dutch MRA for drinking water);
- Capture details on software or programming code for performing the risk characterization and the associated sensitivity and uncertainty analyses in a second advanced MRA document or separate white papers.

General principles from the Appendices should be captured into the appropriate chapters. Also, where appropriate, some of the detailed information from the chapters and appendices could be better placed into a protocol (as mentioned above in support of choosing appropriate dose-response models for example) and more advanced MRA documents. Separate white papers could be written to expand on detailed mathematical advances or uses for MRA in the future. These changes would improve the flow of the information.

With such modifications, this document could be entitled, *Introduction to Microbial Risk Assessment*. It could then be used in the same manner that the “Red Book” for carcinogenic risk assessment is used, as a foundation document for MRA.

2. Charge Question 2 – Planning & Scoping and Problem Formulation (Chapter 2)

Please comment on the utility of this chapter to ensure that risk assessments are adequately conceptualized and planned appropriately to address risk management’s issues. Please provide any recommendations for enhancing the utility of this chapter.

Please comment on any enhancements or expanded guidance needed to allow users to prepare and conduct risk assessments to address a broad range of types of risk management questions. Examples of types of EPA uses of MRA may be:

- a) approaches to mitigation of environmentally-based microbial pathogen exposure risks;*
- b) determination of acceptable health risks;*
- c) identification of different exposure factors/routes;*
- d) identification of microbial-based hazards in disease outbreaks;*

- e) *development and prioritization of research needs;*
- f) *competing risks ranking.*

2.1 Utility of Chapter to Ensure that Risk Assessments are Adequately Conceptualized and Planned Appropriately

Overall, this chapter provides a high-level discussion of how to plan and conduct an MRA. The structure described in this chapter, which involves formulating the problem and scoping out the entire process is excellent. It is particularly important in risk assessments to very specifically write down the questions that are being addressed and to develop a plan for addressing them. This approach applies to MRAs but also to nearly any technical investigation. The discussion of components in the conceptual model narrative were listed and concisely discussed, and in general, this chapter is well-written. The overall approach is sound and logical. It is particularly helpful to acknowledge up front that the conduct of an MRA is an iterative process. As the investigation/assessment proceeds, new information may point the investigator in a different direction, and the overall plan will be adjusted accordingly.

2.2 Recommendations for Enhancing the Utility of the Chapter

This chapter contains a good collection of common definitions that are unique to this field. An “outsider” to the MRA field might find this helpful in understanding the process. One recommendation to improve this chapter is to:

- Include some additional clarification to indicate when stakeholders should be consulted in the process, and whether the result of a planning/scoping and problem formulation exercise would be subject to external review.

The chapter could be improved if the diagrams were changed. For example, EPA has a general logic-diagram format used in drinking water regulations that is very helpful. Starting at the top, one proceeds in a downward direction, following a particular arrow. If there is a decision (yes/no) this is shown as a diamond, with arrows leading away from the corners of the diamond depending on the outcome of the decision. If there is an iteration, the arrow is shown looping back around to the starting point. Most of the figures in this chapter do not follow the standard logic-diagram format and if they were changed to this format, this would help tie all the pieces together to get to the end product of planning/scoping and problem formulation. The Committee recommends:

- Formatting all the diagrams in the chapter to the standard logic-diagram format.

3. Charge Question 3 – Exposure (Chapter 3)

Please comment on any additional exposure tools, methods, or approaches that should be included to ensure a robust approach to adequately determining the microbial occurrence and human exposure factors relevant to health risks from water. This includes support for the estimation of the magnitude, frequency, duration, and also additional types of exposure to microbial pathogens by the water route, as well as the range of characteristics of the exposed population and their exposure profiles.

The Exposure chapter of the draft MRA protocol is a relatively short chapter in the overall document. The chapter has a good, concise discussion of the key issues related to exposure assessment and its role in the overall risk assessment. Points that are (properly) emphasized include the ideas that the life cycle and ecology of microorganisms are critical points for understanding the exposure pathways that ultimately lead to an exposure assessment. The current document also notes that the exposure duration and the population characteristics are important variables in assessing overall exposure. Exposure assessment is often very venue- and microbe-specific and previous EPA MRA examples could be included here, such as that performed for the *Cryptosporidium* risk assessment. This example would illustrate the exposure issues that need to be considered as well as delineate the type of specificity and quantitative data that are needed.

In addition, recently published results on shower biofilms (Feazel, et al. 2009) raise questions about the extent to which an MRA can or should be extended to cover exposures that have not been considered previously or recognized as problems for water-borne pathogens. This also included pathogens such as *Legionella*. Incorporating “novel” routes and opportunistic pathogens may require new data for a number of variables, but ignoring these routes could result in unrealistic MRAs for some pathogens and some populations.

3.1 Additional Exposure Tools, Methods, and Approaches

The layout of the entire document is based on the breakdown shown in Figure 7 (p. 32 in the draft document), entitled “Analysis Phase Microbial Risk Assessment for Pathogens.” This chapter is concerned with the bottom three boxes on the left side of that document, called “Occurrence, Exposure Analysis, and Exposure Profile”. The profile is the net result of all the work that precedes the bottom line of the characterization of exposure. Despite its extreme importance to the MRA, the exposure profile is given inadequate treatment in this chapter, compared to the rest of the document. Uncertainty analysis reported in the literature on drinking water MRAs has shown that exposure assessment is the primary factor driving the distribution of risk outputs; thus it remains a very important aspect of the MRA. Two examples from the literature are cited and explained in some detail, but the reader is left to ascertain what constitutes an appropriate statement of the exposure profile and the significance of generating the exposure data. The examples would be much more valuable if the general principles were explained in more detail; this section is too general to be particularly useful. The Committee recommends:

- Bolstering the discussion of the exposure profile.

Exposure assessment for water applications will likely be far more complex in the future than is portrayed in this chapter. Throughout the chapter, the focus seems to be on natural water systems, where the human exposure is likely to occur through swimming or other recreational activities, i.e., where there is direct contact with raw untreated or insufficiently treated water. The protocol is supposed to be useful for that situation, but it must also be flexible enough to include more complex situations, such as assessing the risks associated with drinking water, where human exposure to pathogens has been attenuated by environmental factors or water treatment. MRA in drinking water is far more complex than MRA in recreational settings because the drinking water passes through a number of barriers before the water reaches the

consumer. The subject of drinking water and the presence of these barriers are not discussed in the MRA document.

As the unit processes in a water treatment plant are designed to remove or inactivate pathogens, their role in preventing or minimizing human exposure to waterborne pathogens must be incorporated into the exposure assessment. This has been done previously for drinking water rules like the *Surface Water Treatment Rule* and more recently, the *Long Term Enhanced Surface Water Treatment Rule* (Haas, et al. 1993 and Regli, et al. 1991). How the treatment unit processes are configured also plays an important role in defining the strength and reliability (aided by redundancy) of the overall treatment barrier (ASCE and AWWA, 1990). There may be multiple filters feeding into a common header (in which case, each filter operates independently of the others in a “parallel” configuration). In the case of filtration followed by disinfection, the unit processes are in series, i.e., one step (filtration) followed by the next (disinfection); the unit processes may operate independently of each other in a series configuration, but not always. The concepts outlined in the ASCE and AWWA (1990) design manual have been used and demonstrated in particle counting studies and to establish regulatory log removal credits for *Giardia* and *Cryptosporidium* (Sakaji, et al. 1996). The statistical techniques used in this work are applicable to evaluating human exposure to pathogens in drinking water in large water treatment plants with multiple unit processes. The Committee recommends:

- Adding a discussion of drinking water exposures and the complex issues associated with doing so, including water treatment barriers;

Aside from drinking water, the document does not include exposure assessments associated with the use of reclaimed wastewater, recycled water, and gray water. All of these are important sources of water that will be used to amend current water supplies and/or improve water efficiency. Although the USEPA does not have current national programs in these subject areas, state agencies, which have recycling programs have used MRAs in their development of public policy for water recycling and will use the USEPA’s MRA document for this purpose. There is a body of published literature in the area of MRA that the Agency can cite, for use of recycled wastewater in agricultural irrigation, swimming, and landscape irrigation practices (Asano, et al. 1992; Soller, et. al. 2004; Rose et al., 1996). Because the terminology of reclaimed wastewater, recycled water, and gray water will be unfamiliar to many, these terms will need to be defined and explained in detail. Given the recent cross connection between a reclaimed wastewater irrigation line and potable water supply line in Coomara, Australia (this is not the first time; there have been cross connection incidents in California with recycled wastewater, none associated with a waterborne disease outbreak), this remains a route of exposure wherever water conservation occurs. The Agency may want to add a footnote about this. The Committee recommends:

- Adding a discussion of exposures from the use of reclaimed wastewater, recycled water, and gray water.

Another weakness of this chapter is that it focuses on endemic exposure risks and not episodic exposure risks. An exposure assessment in drinking water will need to consider all the

events leading to exposure and account for the likelihood of those events occurring. Pathogens in treated water supplies typically occur episodically rather than endemically. A series of seasonal events (such as a rare storm event on a watershed) can lead to a significant change in raw source water quality. If this change is severe enough it can lead to the overload and subsequent failure of a treatment system. However, the failure of water treatment systems is an extremely rare event because the events leading to it are not frequent and with adequate on-line real time monitoring are easily avoided. The low frequency of such failures needs to be captured and included in the drinking water exposure assessment. The Committee recommends:

- Adding a discussion of episodic exposures.

Connecting exposure assessment to management strategies is important for drinking water in particular. Thus another element of the assessment could incorporate a hazard assessment and critical control point analysis (HACCP) to determine where the “weak” or critical control points are, where the possible concentrations of pathogens and potential for exposure are greatest, and where barriers are needed and should be monitored (or strengthened) to prevent an outbreak. In order to prevent further delay in publishing this document, the HACCP concept could be identified in this document and developed further in the detailed protocol.

This chapter is the shortest of all the chapters, but the brevity is largely due to the omission of several important points. As noted above, the chapter does not include anything about the drinking water pathway as a possible exposure route for microbial risk; it is essential that this be addressed in all parts of the chapter. Another serious omission is a lack of discussion on the use of indicator organisms instead of direct measurements of pathogens. Indicator organisms or surrogates are used extensively in environmental risk management as indicators of disinfection efficacy and provide many of the temporal and spatial data sets on sources, transport and fate, as stated in the analytical methods chapter of Haas, Rose, and Gerba (1999). This discussion should start with the four characteristics of a good microbial surrogate as referenced in Kay and Fricker (1997). The discussion should then evolve to explain how the choice of using indicator organisms contributes to the uncertainty. Situations in which indicator organisms are more or less likely to be present than the true pathogens of concern should be addressed in this chapter. The Committee recommends:

- Adding a discussion of using indicator organisms instead of direct measurements of pathogens.

3.2 Suggestions for Improvement

The Committee’s suggestions reflect the comments above about omissions and weaknesses. The early part of the chapter should emphasize not only the similarities but also the differences that exist between chemical exposure assessment and microbial exposure assessment. Exposure assessments for microbes can be substantially more challenging than it is for chemicals. The delineation of these differences will highlight the data needs. The lack of available data is a major limitation in assessing exposure, or the likelihood of exposure, in the development of any MRA, so data needs should be highlighted since it adds considerably to the uncertainty. If

possible, giving specific suggestions about possible data sources, or how data might be obtained, for the performance of an MRA would be useful. The Committee recommends:

- Emphasizing not only the similarities but also the differences that exist between chemical exposure assessment and microbial exposure assessment;
- Highlighting data needs for microbial exposure assessment;
- If possible, giving specific suggestions about possible data sources, or how data might be obtained, for the performance of an MRA;
- Incorporating Appendix F, which is only one page in length, into this chapter; it could be done as a “text box” if the authors think that it is disruptive to the overall flow.

The chapter can be improved by adding examples of MRAs throughout the chapter. These include:

- MRAs used in drinking water exposures;
- Recently published MRAs used to guide beach closures and recreational exposures.

The Committee recommends that the discussion regarding analytical methods and the interpretation of results needs to be expanded and given its own section. Such a section would provide a better presentation regarding the interpretation of occurrence results, since different types of assays are used to enumerate pathogens. As noted earlier, the exposure assessment is the greatest source of uncertainty and the hazard assessment and critical control point analysis (HACCP) will probably point to the interpretation of the occurrence data as contributing the most to the overall uncertainty of the MRA. Some of these assays are designed only to detect and enumerate infectious pathogens, whereas others provide a response based on DNA or antigen (protein components) presence that does not differentiate between viable, infectious, and nonviable pathogens.

The discussion on exposure associated with methods is confusing and should be reorganized and further related to the other chapters (e.g., the dose-response chapter). An example of this is found in the discussion on page 45 under the heading “What is the Level of Pathogens in the Water Body?”. The sentence that begins with “Assays used to quantify pathogens yield variable...” identifies three major points. These points relate to the analytical methods; the variable recovery rates associated with the assays; detection limits; and the fact that the assays may not provide information on the viability of pathogens, which affects their ability to infect humans. While these are important points, their importance is lost in the subsequent discussion on evaluating the efficacy of treatment. The example of the oocyst excystation assay not providing information on the infectivity of the trophozoites is accurate from the standpoint of evaluating the effectiveness of UV as a treatment technology, but misses a larger point. If the assay used to enumerate the oocysts in the Dupont human infectivity study (1995) provides the same level of enumeration accuracy (with the associated limitations) as the water sample assays for oocysts, then the major difference with excystation studies used to evaluate UV (early studies), would be the relative level between total count of oocysts and infectious oocysts. Thus what the discussion misses is that there may be a change in the relative ratio of infective, viable, and nonviable oocysts in the sample between the source of the oocysts and the raw water intake. The estimates of human infective dose used in developing the dose-response relationship have

uncertainty associated with the dose. Freshly-harvested oocysts were used as the inoculums in the human challenge studies and are often used in disinfection studies, yet the age of the oocysts in any given water sample can vary widely, as could the distribution of viable and infective oocysts. This difference leads to part of the uncertainty in the interpretation of the data, and thus the specific assumptions need to be clearly stated and used in exposure assessment. When new methods are introduced, such as cell culture techniques to enumerate the number of infectious oocysts in water samples, they may allow refinement of the dose-response relationship (Slifko, et al. 1997; Slifko, et al. 1999; Slifko, et al. 2002). This refinement can then be used to improve future exposure assessments.

The subsequent paragraph jumps to a discussion of how environmental factors can affect the numbers of microbes and spectrum of microbes including bacteria and viruses. These analyses often have the opposite problem from oocyst measurements, as culture techniques may underestimate the dose. It is well known that culture techniques routinely used in the laboratory can not address the presence of all viable bacteria or viruses. It should be further pointed out to the reader that even the bacterial assays depend on the “state” of the bacteria as some may be in a stressed or quiescent stage and while non-culturable can be infectious once ingested. Thus the exposure is underestimated as is the risk.

The analytical methods for detecting microorganisms in water are probably the biggest challenge and represent the largest source of difference between chemical and microbial risk assessments. The microbial methods include microscopic techniques that do not rely on the viability of the microbe (*Cryptosporidium* and *Giardia*). The method detection limits for microbial assays are written as less than one organism per volume of water processed (which might be considered analogous to one atom of a chemical contaminant in a volume of water), generally without consideration of recovery efficiencies or false positive/negative rates. The approach to establishing minimum limits of detection and practical quantitation limits for microbial methods is unlike the approach taken for analytical methods used to enumerate chemical concentrations. While the assumption of one organism per volume of water sampled as a method detection limit may work for some microbial assays, it is not valid for all assays. For example, the highly variable recovery rates for *Giardia* and *Cryptosporidium* may be affected by the amount of processing the sample goes through before the enumeration step. In turn, this affects the reliability and reproducibility with which one oocyst or cyst can be enumerated in a sample volume. Poor reproducibility contributes to increased uncertainty as the concentration approaches the minimum detection limit.

Later in the chapter the statement “Correction of oocysts counts for viability...” indicates that correcting for viability has little impact on the concentration distribution. This statement needs to be clarified. Does this mean the shape of the distribution doesn’t change, but the position of the mean does? If so, assessing viability is still important, as the magnitude and strength of the treatment barrier may not need to be as great as regulations dictate. The statement seems to contradict the earlier arguments regarding the importance of viability for assessing treatment efficacy.

In summary then the Committee recommends:

- Bolstering the discussion of the exposure profile;
- Adding a discussion of drinking water exposures and the complex issues associated with doing so, including water treatment barriers;
- Adding examples of MRAs used in drinking water exposure scenarios;
- Adding a discussion of exposures from the use of reclaimed wastewater, recycled water, and gray water;
- Adding a discussion of episodic exposures;
- Adding a discussion of using indicator organisms instead of direct measurements of pathogens in water.

Other suggestions for improving the chapter include:

- Emphasizing not only the similarities but also the differences that exist between chemical exposure assessment and microbial exposure assessment;
- Highlighting data needs for microbial exposure assessment;
- If possible, giving specific suggestions about possible data sources, or how data might be obtained, for performing an MRA;
- Incorporating Appendix F, which is only one page in length, into this chapter, possibly as a “text box” if the authors think that it is disruptive to the overall flow;
- Adding examples of recently published MRAs used to guide beach closures and recreational exposures;
- Expanding the discussion regarding analytical methods and the interpretation of results with a section heading.

4. Charge Question 4 – Human Health Effects (Chapter 4)

Please comment on any additional scientifically accepted dose-response models (including advanced and validated threshold, empirical, or mechanistic models) which should be included as tools for determining human dose-responses from waterborne exposures via oral, inhalation, and dermal routes, especially for low dose extrapolation. Please comment on whether any specific animal or in vitro dose-response protocols, models, and methods should be included in this chapter. If so, please describe their applications and limitations in establishing human dose-response curves.

4.1 Scientifically Accepted Dose-Response Models

The discussion of scientifically accepted dose-response models in the chapter, when combined with Appendix G, was comprehensive and thorough. General principles from Appendix G are critical to interpreting the chapter and therefore should be merged into the chapter. However, the Committee strongly recommends that the material in Appendix G be rewritten by an expert statistician for accuracy in its description of the extant literature and methods, and for appropriate continuity between the discussions of the various statistical techniques.

Description of the data sets used for the dose-response curve fitting and the variability around the parameters should be included, and can be used further in MRA during uncertainty analysis. This characterization of the data sets may allow the reader to better understand how the quality of the data set and how the uncertainties in the data set affect the confidence one has in the dose-response curve. These details should include information about the microbial and host factors, such as pathogen strain and virulence, and host age. Extrapolations to low dose always bring many uncertainties, because often, no data at the low doses are available. The dose-response data sets for bacteria often reflect this lack of data at low doses, whereas those for viruses and parasites usually do include some low doses. The confidence levels surrounding the best-fit curve broaden with extrapolation to the low doses, and this concept should be included as one of the uncertainties surrounding the data. Furthermore, uncertainty is introduced when one extrapolates from information derived from a specific setting to the larger and more general circumstance. Take, for example, a specific study, which uses a specific experimental pathogen strain of microbe, and examines the consequences in a defined and specific human group or population. When generalizing from this specific study the assumption may be made that this microbe was representative of all of the pathogenic strains of the microbe, and that the human population that was studied was representative of the entire human population. This may not be true, and the uncertainty introduced by this assumption should be mentioned. The Committee recommends:

- Adding a discussion of uncertainty in dose-response modeling arising from data sets, low dose extrapolation, and microbial and host factors.

4.2 Animal Dose-Response Models

A future research need is the exploration of the mathematical description of the dose-response functions associated with variations in pathogen virulence, multiple doses, and mixtures. Animal models will provide the opportunity for advancing an understanding of the dose-response process. While it is acknowledged that many animal feeding studies do not meet the criteria for developing statistically best-fit dose-response models, this chapter should include some discussion of animal models that would be useful for the future.

The gnotobiotic piglet model is one such model. It has been used for a number of human enteric (diarrheal) pathogens such as *Campylobacter jejuni*, *Shigella dysenteriae*, *Salmonella*, *Cryptosporidium*, *Isospora*, *Helicobacter pylori*, and *Escherichia coli* (Law et al., 2009; Jeong et al 2010). This model has been found to be useful for studying different manifestations of human disease. Gnotobiotic piglets have also been used to study a spectrum of rotavirus and even Norovirus isolates (Zhang et al., 2008). The application of this specific model is dependent upon the pathogen and the health outcome of interest. A broad range of other animal models ranging from the worm *C. elegans* to primate relatives of humans have also been studied to ascertain mechanisms of pathogenicity and microbial virulence. Further use of these models should be exploited to gain a better quantitative understanding of dose-response relationships relative to microbe-host-environment interactions with particular emphasis on susceptible populations. Of particular relevance would be those studies focused on immuno-compromised/incompetent and aged populations for which models such as nude mice have yielded important mechanistic insight and could be further extended to dose response/risk assessment relationships.

The data are scanty for many human pathogens, especially considering the spectrum of health effects upon which a modeling exercise must rest. Considerable information relevant to some pathogens (*Cryptosporidium*, *E. coli*) is available, but little exists for many other pathogens. These scientific gaps will need to be filled and in most cases, receptive and competent animal models will need to be used.

4.3 Human Health Outcomes

Responding to the two charge questions on mathematical modeling of health outcomes and animal or *in vitro* models could have been more vigorous had the health effects of interest been defined. A better description of the human health outcomes associated with exposure to the wide range of environmental pathogens should be included in a very specific chapter devoted to this topic. A major observation was that this chapter contained little discussion of the health effects of interest and how mathematical approaches could be used to incorporate these effects into probability models or disease transmission models; the human health outcomes were not defined or delineated in sufficient detail. The majority of the chapter focused on dose-response analysis, obviously an important topic, but did not define the health effects of interest *per se* to which modeling should be applied. For example, viral hepatitis may be a waterborne disease, but the word “hepatitis” is only mentioned in the entire document three times – once in a chart, once in an explanation that human hepatitis E is similar to the porcine variant; and once in a discussion of milder disease in children. The exposure models are elegant, but modeling must be grounded in factual data to have authenticity and to be useful to the reader of this document. The Committee recommends:

- Making the dose-response section a separate chapter from the description of the health effects;
- Expanding the discussion of health effects to include defining and delineating health outcomes.

The first section of this chapter on health effects (4.1) mentioned a number of health effects “elements” that should be considered during risk assessment. These elements included duration and severity of illness, the morbidity and mortality and long-term health effects, transmission to others, and quality of life. These are described in a bit more detail over a 2-page section before the dose-response analysis overview (4.2) begins.

The section on health effects does not include a description of some of the major health syndromes. These should include watery diarrhea, nausea and vomiting, illnesses similar to influenza, dysentery, hepatitis, meningitis, and others. Some inkling of these syndromes is given in the subsection that describes chronic sequelae (4.1.3) and lists some delayed effects of infection. However, there is no corresponding section on acute effects, and the list of chronic effects is illustrative, but not comprehensive. With such delineation of chronic and acute effects, it might be easier to identify where models, based in sound science, exist and where they do not. The Committee recommends:

- Including a description of the major health syndromes and delineating the chronic and acute effects.

Earlier in the document, in section 2.2.4 (page 24) on the Scope of problem formation, the suggestions are made that the scope should include “Which infectious disease hazard is being addressed; ...which human populations will be included in the risk assessment; ...and what health outcome or endpoints are addressed by the risk assessment, including how the health outcome is measured.” The point is made in that section that the scope of the assessment (infection, disease symptom/s, mortality) must be defined. These different outcomes are all health effects to which the modeling can be applied. The document could be improved by providing examples of the health effects of interest, and how they have been used in prior risk assessments to give the reader a sense of the literature. Were this suggestion to be followed, a response to the charge questions with more detail could be provided. The Committee recommends:

- Providing examples of the health effects of interest, and how they have been used in prior risk assessments.

The section in the Health Effects chapter that begins on page 56 is an admirable compendium of the mathematical models which have been, or could be, used to model the effects of fairly generic exposures in a population. These models address the extent or likelihood of a general health effect in the population, not the modeling of the specific human health effects of interest. Human health effects information would allow a more robust analysis of the models that may, or may not, exist for specific health effects. Table IV of the chapter, on pages 69-70, provides information on pathogens and models used to describe their effects. An additional column (or a separate table) should be included that delineates the anticipated health effects of these pathogens. The Committee recommends:

- Adding specific health effects information in the compendium of mathematical models.

In the section on human health effects, there is no mention of the spectrum of severity of health effects that may occur in a population. While the median health effect of some infections may be minor, some individuals - only some of whom may belong to a susceptible population - may suffer uncommon, yet severe effects. By way of illustration, most children with diarrhea in the US have mild illness, so the severity of the average or median case of diarrhea is minor. However, some children with diarrhea become dehydrated and require admission to hospital, and a small number of these children will die. Thus the spectrum of the severity of the illness is broad, ranging from subclinical infection to death, while the severity of the median case is of minor consequence. The Committee recommends:

- Adding a discussion of the spectrum of severity of health effects that may occur in a population.

In addition, the health effects may include a spectrum of syndromes caused by a single microbial agent. An example of this variation can be seen with some enteroviruses, which most often cause diarrhea but also can cause meningoencephalitis (infection of the brain) and pericarditis (inflammation of the pericardium, which encloses the heart). While the diarrhea is typically not life-threatening, the meningoencephalitis may easily result in hospitalization, and the pericarditis may result in not only hospitalization but also life-long adverse effects. It would

be useful for the document to further highlight this point, perhaps in an example, to illustrate not only the severity but the spectrum of human health outcomes that are possible. The Committee recommends:

- Adding a discussion of the spectrum of syndromes caused by a single microbial agent.

A nexus of scientific advances is likely to substantially improve our understanding of the dose-response relationship between drinking water pathogens and human health outcomes in the near to mid-term future. These advances include:

- The development and adoption of real-time pathogen detection in drinking water systems, spurred by homeland defense concerns;
- The identification of specific genetic susceptibilities to microbial pathogens via rapid advances in genomic medicine; and
- Improvements in surveillance systems which can better detect and follow human health syndromes, and specific disease, in the US population.

The first will allow us to understand the magnitude of, and variance in, waterborne microbial pathogen occurrence using novel technologies that bypass the limitations of current methods. Real-time molecular or chromatographic monitoring will undoubtedly reveal exposures that we would not otherwise be aware of. Our current system of episodic or infrequent sampling, and detection via methods that depend upon pathogen growth, act as constraints in understanding the occurrence of pathogens.

Genomic science is likely to identify specific genetic vulnerabilities to more microbial agents found in water, just as it is currently identifying the genetic basis for other infectious diseases such as Noroviruses, human immunodeficiency virus (HIV), severe acute respiratory syndrome (SARS), and Epstein-Bar virus (Lindesmith, et al. 2003). Finally, specific susceptible populations beyond our current understanding will be identified. We currently recognize infants and children, the elderly or pregnant, and those immuno-compromised by disease or drugs as susceptible to infectious agents (see more in the section below). These advances will help us to understand the full range of population-wide health effects as well as effects in specific sentinel populations.

In aggregate, improved occurrence data and improved outcomes information should lead to far more robust risk assessment.

4.4 Susceptible Populations

The chapter on Problem Formation includes a subsection on susceptible populations [“Initial host characterization” pages 38-40, section 2.3.2] that is closely related to this chapter on Health Effects; the Committee recommends that some or all of that subsection should be moved to, or concisely reiterated in, this chapter. Certainly different populations may be affected by different routes of exposure. The example is given of behavioral elements, such as the ingestion of raw sea food, which is the critical route of exposure for some diseases. However, much of the discussion about susceptible populations in this section is relevant to how diseases

may be differentially expressed in susceptible populations. It is clear from the literature that certain populations including the elderly, immuno-compromised people, and young children are more susceptible to adverse outcomes (as seen with outbreaks of *E. coli* 0157: H7 and AIDS patients and *Cryptosporidium*). Currently there are no data that demonstrate that this susceptibility is a result of changes in dose-response functions. It appears likely that the increased susceptibility is related to an attenuated host response, once the infection has been initiated. The dose relationship between infectivity and age (young and old)/immuno-compromised populations is ambiguous. There is a need to break down the host response into various components, including timing or onset of infection and disease severity. Such host response concepts have been acknowledged for food-borne bacterial infections (Buchanan, et al. 2000) and need to be considered for the pathogen-host-environment interaction in MRA protocols. The Committee recommends:

- Moving, or concisely reiterating, some or all of the susceptible population subsection in Chapter 2, to this chapter.
- Adding a discussion of host response concepts such as timing or onset of infection and disease severity.

4.5 Quality of Life

The Committee does not believe that the quality of life discussion belongs in this document. Quality of life is not part of the risk assessment process, but rather could be part of the cost-benefit analysis. Although it could be used for comparison of different hazards and could be used as a metric for risk management, this is not the approach that EPA has used in the past. The Committee recommends removing this discussion from the document.

5. Charge Question 5 – Risk Characterization (Chapter 5)

Please comment on any improvements needed to achieve the necessary outputs or linkages between the components of the problem formulation, exposure, and health chapters to make risk characterization easier to conduct. Please comment on any additional approaches or methods to address uncertainty, variability, and sensitivity analysis of the various pathogen, health and exposure factors used in risk characterization.

5.1 Improvements to the Linkages between the Planning & Scoping and Problem Formulation, Exposure, and Human Health Chapters

This chapter is a good summary of risk characterization and of the models used in this area. It is written clearly and concisely. However, a number of improvements should be made to strengthen this important chapter. The Committee recommends:

- Adding summaries at the ends of Chapters 3 and 4 about what pieces of information need to be brought forward from those respective chapters and folded into a risk characterization.
- Summarizing the elements that need to be drawn from the earlier chapters and incorporated into a risk characterization at the beginning of Chapter 5.

Although these changes might seem simplistic or repetitive, they would help clarify the links between the components of the risk assessment and would improve the continuity of the document as a whole.

The discussion of models occurs both in Chapter 4 (relative to dose-response) and in Chapter 5 (relative to risk characterization). This situation is somewhat confusing to the reader, since it is not always clear if the same or different models are applicable in each instance (i.e., does one use the same tool(s) to model dose-response and to characterize uncertainty and variability?). It also ends up being repetitive. The Committee recommends:

- Trimming unnecessary detail and redundancy about the models in these chapters (perhaps, capturing the detail in a second more advanced MRA document and/or technical white papers);
- Clarifying explicitly the different roles that the (same or different) models play in each of these aspects of the risk assessment. These changes will ensure that the reader understands what needs to be accomplished by the modeling exercise in each step.

The Committee recommends that the Agency not use the terms “static” vs. “dynamic” modeling. These terms are not generally accepted in the MRA field. Both approaches described can be dynamic. We note that the Susceptible, Infected, Recovered (SIR) model takes into account the contagious nature of pathogens and of continuing, dynamic transmission. Many SIR models require a substantial number of assumptions to be made in order to derive a risk output.

The Risk Characterization chapter should also explicitly refer back to the problem formulation, planning and scoping described in Chapter 2, especially Sections 2.1 and 2.2. It is important for the risk assessor to state at this stage whether, and how well, both the Statement of Concern and the Statement of Purpose and Objectives that were identified up-front in the risk assessment were, in fact, addressed. Although the topic of problem formulation is included as one of the items that should be addressed in the risk description summary at the end of the chapter (Section 5.5), it should be given greater emphasis elsewhere in the chapter as well. The Committee recommends:

- Adding text to explicitly refer back to the problem formulation, planning and scoping described in Chapter 2, especially Sections 2.1 and 2.2.

The title of Appendix D - MRA General Concepts, is misleading. One would expect this section to address principles and tools by which aspects of exposure, hazard, and dose-response assessment would be conducted. In fact, its entire focus is on Risk Characterization, but Chapter 5 never makes reference to its existence or content. The Committee recommends:

- Placing some of the topics that are in Appendix D that are not already addressed in Chapter 5 (i.e., the topics covered in Sections D.4-D.10), in an overview/summary format within Chapter 5.

5.2 Uncertainty, Variability, and Sensitivity Analysis

Uncertainty, variability, and sensitivity analysis are important and deserve emphasis in this document. Section 5.4, which discusses these issues is good, and does not omit any significant approaches or methods. The Agency may choose to re-format this document such that this chapter presents the general principles of uncertainty, variability, and sensitivity analysis and the detailed discussions of the uncertainty, variability and sensitivity analyses required for a credible and complete risk characterization should be placed in the detailed follow-up document and/or, separately, in white papers on these topics.

In any case, this document should acknowledge, and describe in an appropriate level of detail, the principles and practices regarding uncertainty, variability and sensitivity analysis presented in existing Agency documents that are, or could be, relevant to the conduct of MRAs. These include *Guiding Principles for Monte Carlo Analysis* (USEPA, 1997); *Report of the Workshop on Selecting Input Distributions for Probabilistic Assessments* (USEPA, 1999); *Guidelines for Preparing Economic Analyses* (USEPA, 2000a); *Using Probabilistic Methods to Enhance the Role of Risk Analysis in Decision-making with Case Study Examples* (External Review Draft) (USEPA, 2009). This latter document includes a case study on the *Two-dimensional Probabilistic Risk Analysis of Cryptosporidium in Public Water Supplies, with Bayesian Approaches to Uncertainty Analysis* which was conducted in support of the development of the *Long Term 2 Enhanced Surface Water Treatment Rule*. This case study could serve as one of the case examples that the Committee is recommending to be added to the revised document. With the publication of so many guidelines, it would help to attain some degree of consistency in public policy if frameworks and approaches to risk assessment were consistent. This consistency could be achieved by referencing and using existing guidelines, noting exceptions or changes in the guidelines as dictated by legislative or executive direction. Guidelines are rarely recalled or revised based on new science, so changes to previous guidance need to be clearly and duly noted to improve the transparency of decision making within the agency. The Committee recommends:

- Acknowledging, and describing in an appropriate level of detail, the principles and practices regarding uncertainty, variability and sensitivity analysis presented in existing Agency documents that are, or could be, relevant to the conduct of MRAs.

The uncertainty analysis can be done using a Monte Carlo approach to examine each element in the MRA to determine contributions to overall risk outputs. Those factors (for example in exposure assessment) that may be contributing to most of the uncertainty of the final result may pinpoint where more data are necessary or where risk management decisions should be focused in the development of policy. Applying the HACCP system which has been used in food safety could be useful as part of this activity, whereby the risk characterization could be tied to best management approaches.

5.3 Other Recommendations

Overall, the Committee felt that Chapter 5 could benefit from significant editing to better focus the chapter and to assure that the essential elements of the chapter are not lost in the

tangential discussions and excessive detail. Specifically, the Committee recommends the following:

- Edit Section 5.1.1 on Historical Context (minimize the verbiage) with the exception of the last paragraph on EPA policy;
- Shorten Section 5.1.3 on Parsimony to one paragraph which defines the concept, and to state how to make the determination (drawing on the concepts outlined in Appendix G.1);
- Change Section 5.1.2 to be consistent with EPA's *Risk Characterization Handbook* (USEPA, 2000b). (Because the document we were asked to review is primarily a document for EPA use, the terminology for risk assessment, and particularly for Risk Characterization, should be consistent with EPA's risk assessment terminology. In some places in the document, the terminology appears to reflect the International Life Sciences Institute (ILSI) Framework for Microbial Risk Assessment rather than EPA's own risk assessment terminology. For example, EPA's Handbook does not define Risk Characterization as consisting of two major steps – risk estimation and risk description.)
- Create a companion to Figure 9 that includes the same set of models but summarizes the pros and cons of each model choice (or the situations to which each model type is best suited);
- Shorten the discussion on the various model types to focus on the pros and cons of each model type and when they should be used;
- Remove the excessive detail on the models, such as Table 6 and Figure 12;
- Shorten Section 5.2.3 or move it to a second more advanced MRA document and/or white papers. In particular, the lengthy literature review on Bayesian models on pp. 84-86 should be removed and that section should be reduced to one paragraph.

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APPENDIX – EPA CHARGE QUESTIONS



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MEMORANDUM

SEP 16 2009

SUBJECT:

Approval of Final Charge Questions for Science Advisory Board (SAB) Review of draft ^{OFFICE OF} Microbiological Risk Assessment Protocol for Water Media _{WATER}

FROM:

Dr. Edward Ohanian
Division Director
Health and Ecological Criteria Division
USEPA, Office of Water, Office of Science and Technology

TO:

Dr. Vanessa Vu
Director
Science Advisory Board
USEPA, Office of Research and Development

The Office of Science and Technology (OST), Health and Ecological Criteria Division (HECD) approves and submits the Microbial Risk Assessment (MRA) Protocol for Water Based Media for release by the SAB to their expert review group for technical review. Also, OST/HECD approves the final SAB Charge Questions (see attachment) for the expert reviewers to respond to in the assessment of the draft MRA Protocol. The Charge Questions are appropriate and focus on areas of the Protocol which OST/HECD wishes to gain further improvements or insights, and to correct possible technical errors or omissions. This effort will make the final MRA Protocol a more useful and comprehensive tool to support future risk assessments.

OST/HECD wishes to thank the SAB for its work in coordinating and preparing for the September 21, 22, 2009 meeting of its technical experts and looks forward to receiving significant guidance from the SAB review to improve the MRA Protocol.

SAB REVIEW OF MRA PROTOCOL

BACKGROUND

Over the past decade, the Office of Science and Technology (OST) in the EPA's Office of Water has been involved in the development of a Microbiological Risk Assessment (MRA) Protocol to better inform persons conducting EPA sponsored MRAs about available approaches, methods, and tools, thus enhancing the capability of the assessors to prepare successful products. Initially, OST enlisted the International Life Sciences Institute through a cooperative agreement to help develop a MRA framework based upon the specific or unique risk assessment factors that risk assessors need to consider in conducting MRAs in water media. Subsequently, the OST sponsored a number of workshops to identify existing or generally accepted developmental approaches, tools, methods, and procedures for application in populating the framework to establish the protocol for conducting MRAs, especially for water-based media (drinking water, recreational water, biosolids, shellfish growing water, etc.).

At this time the OST has developed a draft MRA Protocol document that it believes captures the essential components for risk assessors to use to successfully conduct microbiological risk assessments in water media. The current Protocol focuses only on risk assessment components and does not broadly consider all aspects of risk management or risk communication although it is recognized that these features are essential components for conducting a successful risk analysis. After review by the EPA's Science Advisory Board the OST will make essential modifications to the protocol and will then list this document on its website so that it will be available to all EPA staff and contractors involved in risk assessment as well as the general microbiology community.

CHARGE QUESTIONS

The following non-prioritized list of questions to the Science Advisory Board reviewers has been prepared to help EPA's Office of Water, Office of Science and Technology, improve the MRA protocol's effectiveness for users. It is envisioned that the SAB Reviewers will provide new insights and technical additions or modifications to improve the ease of use, technical robustness, clarity, and efficacy of the MRA protocol as a resource for guidance or support in conducting risk assessments. The focus of the MRA Protocol is to support professional microbiologists and risk assessors conducting water-based microbial risk assessments on conventional waterborne microbial pathogens and the water route of exposure.

1. Overarching Considerations:

OST would like this Protocol to provide a comprehensive and robust suite of approaches, tools, methods, and procedures to meet EPA's overall needs in preparing for, and conducting typical MRAs. OST would also like the Protocol to be informative, easy to use and understand, and useful to outside stakeholders (states, communities, utilities, industry, and impacted parties).

Please comment on the following:

- a) utility of the Protocol for meeting EPA's overall needs, particularly on the comprehensiveness and robustness of the Protocol;
- b) flow and continuity within and between chapters;
- c) ease of use and utility for outside stakeholders;
- d) any changes or enhancements to the Protocol to ensure it meets the needs of EPA and outside stakeholders.

2. Planning/Scoping and Problem Formulation – Chapter 2:

Please comment on the utility of this Chapter to ensure that risk assessments are adequately conceptualized and planned appropriately to address risk management's issues. Please provide any recommendations for enhancing the utility of this Chapter.

Please comment on any enhancements or expanded guidance needed to allow users to prepare and conduct risk assessments to address a broad range of types of types of risk management questions. Examples of types of EPA uses of MRA may be:

- a) approaches to mitigation of environmentally-based microbial pathogen exposure risks;
- b) determination of acceptable health risks;
- c) identification of different exposure factors/routes;
- d) identification of microbial-based hazards in disease outbreaks;
- e) development and prioritization of research needs;
- f) competing risks ranking.

3. Exposure – Chapter 3:

Please comment on any additional exposure tools, methods, or approaches that should be included to ensure a robust approach to adequately determining the microbial occurrence and human exposure factors relevant to health risks from water. This includes support for the estimation of the magnitude, frequency, duration, and also additional types of exposure to microbial pathogens by the water route, as well as the range of characteristics of the exposed population and their exposure profiles.

4. Human Health Effects – Chapter 4:

Please comment on any additional scientifically accepted dose response models (including advanced and validated threshold, empirical, or mechanistic models) which should be included as tools for determining human dose responses from waterborne exposures via oral, inhalation, and dermal routes, especially for low dose extrapolation.

Please comment on whether any specific animal or in vitro dose response protocols, models, and methods should be included in this Chapter. If so, please describe their applications and limitations in establishing human dose response curves.

5. Risk Characterization – Chapter 5:

Please comment on any improvements needed to achieve the necessary outputs or linkages between the components of the problem formulation, exposure, and health chapters to make risk characterization easier to conduct.

Please comment on any additional approaches or methods to address uncertainty, variability, and sensitivity analysis of the various pathogen, health and exposure factors used in risk characterization.