

1-12-10 Science Advisory Board (SAB) Drinking Water Committee Advisory Report

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



OFFICE OF THE ADMINISTRATOR  
SCIENCE ADVISORY BOARD

DATE

EPA-SAB-09-0XX

The Honorable Lisa P. Jackson  
Administrator  
U.S. Environmental Protection Agency  
1200 Pennsylvania Avenue, N.W.  
Washington, DC 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 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 met on September 21-22, 2009 to review EPA's Draft Protocol and to discuss the charge questions.

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1           The Committee commends the Agency for all the work undertaken and for taking a  
2 leadership role in the interagency microbial risk group. This MRA document had been in  
3 development for many years and has undergone extensive internal and external review. It is  
4 important for EPA to complete this document as soon as possible as it will likely become an  
5 important document in this area. The key points and recommendations of the Committee are  
6 detailed in the report. Below is a brief summary.  
7

8           Overall, the Committee finds the document to be comprehensive and inclusive of key  
9 information, but believes technical editing is needed to provide concision, clarity, and parallel  
10 structure between the chapters. The Committee also finds that the document does not fulfill its  
11 intended purpose as a “protocol.” A protocol generally implies a set of specific steps that would  
12 be undertaken to perform, in this case, an MRA. This document does not provide those steps;  
13 rather, it serves as an excellent introduction to MRA by describing the conceptual framework,  
14 types of data and models, and the general process for undertaking an MRA.  
15

16           The Committee strongly recommends the finalization and acceptance of this document,  
17 with appropriate modifications. The Committee recommends the following: (a) review and  
18 revision by a technical editor; (b) rename and restructure the document as a Framework or  
19 Introduction to MRA; (c) add more illustrative examples of actual EPA (or other) MRAs  
20 throughout the document; (d) after publishing this document, develop a second, more advanced  
21 MRA document in the near future that would be a true protocol for conducting MRAs and/or a  
22 series of white papers that would address specific technical topics in greater detail. With such  
23 modifications, this document would represent a valuable foundation block in the field of MRA  
24 for the Agency.  
25

26           For the Planning & Scoping and Problem Formulation chapter, the DWC recommends  
27 adding sufficient detail which connects the problem to the MRA implementation via the  
28 framework, with flow charts, figures, and logic trees.  
29

30           Sensitivity analyses of MRAs have shown that the greatest variability in a risk  
31 assessment comes from all the factors involved in defining the exposure. The Exposure chapter  
32 should address the episodic exposures, as these events for example associated with flooding, are  
33 when pathogens and outbreaks may be more likely. Other routes of exposure associated with  
34 biofilms and inhalation should be explored and finally the application of indicator organisms  
35 (source tracking markers etc) can be used to define transport and fate and should be addressed in  
36 this chapter.  
37

38           The Human Health Effects chapter addresses the mathematics of dose-response data for  
39 development of MRA models and the subsequent health outcomes. This should be split into two  
40 chapters. The human health piece should be further developed with more descriptions on the  
41 types of illnesses, the severity of illness, and the specificity of syndromes, including chronic  
42 outcomes and susceptible populations. The dose-response mathematical section in combination  
43 with Appendix G will require statistical expert review to ensure accuracy.  
44



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**NOTICE**

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This report has been written as part of the activities of the EPA Science Advisory Board, a public advisory committee providing extramural scientific information and advice to the Administrator and other officials of the Environmental Protection Agency. The Board is structured to provide balanced, expert assessment of scientific matters related to problems facing the Agency. This report has not been reviewed for approval by the Agency and, hence, the contents of this report do not necessarily represent the views and policies of the Environmental Protection Agency, nor of other agencies in the Executive Branch of the Federal government, nor does mention of trade names or commercial products constitute a recommendation for use. Reports of the EPA Science Advisory Board are posted on the EPA Web site at: <http://www.epa.gov/sab>.

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**Drinking Water Committee**

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1 **ACRONYMS**

2

3

4 CWA Clean Water Act

5 DWC Drinking Water Committee

6 EPA Environmental Protection Agency

7 MRA Microbial Risk Assessment

8 OST EPA's Office of Water, Office of Science and Technology

9 OW EPA Office of Water

10 SAB Science Advisory Board

11 SDWA Safe Drinking Water Act

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31

1 **EXECUTIVE SUMMARY**

2

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

9

10 The Committee finds that the document does not fulfill its intended purpose as a  
11 "protocol." The intended primary audience is the Agency and the secondary audience are  
12 stakeholders such as water utilities. A protocol generally implies a set of specific steps that  
13 would be undertaken to perform, in this case, an MRA. This document does not provide those  
14 steps. However the Agency has done a tremendous amount of work on MRA, is commended for  
15 its leadership in this area, and this compilation serves as an excellent introduction to MRA by  
16 describing the conceptual framework, types of data and models, and the general process of  
17 performing an MRA. Overall, the Committee finds the document to be comprehensive and  
18 inclusive of key information, but believes technical editing is needed to provide concision,  
19 clarity, and parallel structure between the chapters. It is important that this document be  
20 finalized as soon as possible.

21 The Committee recommends the following:

- 22 • Review and revision by a technical editor; in particular Appendix G requires  
23 statistical expert technical review;
- 24 • Add more examples of actual EPA (or other) MRAs throughout the document;
- 25 • Rename and restructure the document as a Framework or Introduction to MRA  
26 rather than a Protocol;
- 27 • Develop a second, more advanced MRA document that would provide a step-by-  
28 step process for conducting MRAs in the near future and/or a series of white  
29 papers that would address specific technical topics in greater detail.

30

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1 *Planning & Scoping and Problem Formulation Chapter*

2           The Committee finds that the Planning & Scoping and Problem Formulation chapter is  
3 generally useful. However, it is missing some information which would allow the reader to  
4 readily follow how the problem formulation is linked to the MRA process, and then to the  
5 desired end products. The linkage between the identified problem, and implementation of the  
6 MRA process could be better outlined through the use of flow charts, figures, or logic trees.

- 7
  - The Committee recommends formatting all the diagrams in the chapter to the  
8 standard logic-diagram format.

9

10 *Exposure Chapter*

11           The Exposure chapter provides a good, concise discussion of the key issues related to  
12 exposure assessment and its role in the overall risk assessment; however some weaknesses and  
13 omissions were identified. Sensitivity analyses of MRAs have shown that the greatest variability  
14 to risk assessment is in defining the exposure. It is therefore vital to consider a comprehensive  
15 range of possible exposures to ensure accurate MRAs. The exposure profile, the sum result of  
16 exposure characterization, is not given adequate treatment in this chapter and is not  
17 comprehensive enough. The chapter focuses on endemic exposures rather than episodic  
18 exposures, which are more likely to occur with pathogens in treated water. The chapter seems to  
19 focus more on risks from recreational exposure as opposed to risks from drinking water  
20 exposure. Drinking water examples, however, should be used throughout, including unusual  
21 exposure routes associated with biofilms and inhalation. The subject of indicator organisms  
22 instead of direct measurements of pathogens is not discussed and should be added. Indicator  
23 organisms are used extensively in environmental risk management and might provide the richest  
24 database on some of the exposure issues associated with sources, transport, and fate. Both the  
25 uncertainty associated with using indicator organisms and situations in which indicator  
26 organisms are more or less likely to be present than the true pathogens of concern should also be  
27 addressed in this chapter.

- 28
  - The Committee recommends that the chapter include a more thorough discussion  
29 of the exposure profile, episodic exposures, drinking water exposures, and the use  
30 of indicators.

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*Human Health Effects Chapter*

The Human Health Effects chapter is largely devoted to dose-response models. The Agency should consider 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, but should be rewritten to be more concise. For EPA’s scientific credibility, it is particularly important that Appendix G be thoroughly reviewed by an engaged, broadly-knowledgeable expert in statistical methods. It is apparent that individuals ensured that their favorite methodological approaches were included in the analysis in Appendix G, but no discussion of the various methodologies nor any scientific overview of the many approaches discussed or advocated is given.

It would be useful to include a discussion of animal dose-response models as a research need in the area of MRA, such as the gnotobiotic pig, which has been used for many human enteric pathogens. 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. In graphical terms, this can be viewed as a widening of the confidence limits around the best-fit curve. These details should include information about the microbial and host factors, such as pathogen strain and virulence, and host age.

The Human Health Effects chapter should be developed further. One major omission in this chapter is any discussion of human health outcomes from microbial pathogen exposure, i.e., the types of illnesses, the severity of illness, and the specificity of syndromes. A discussion about susceptible populations should also be included in this chapter, because susceptibility affects the expression of the disease in humans, e.g., the health effects. The Committee also 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 part of the cost-benefit analysis.

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1 The Committee recommends the following:

- 2 • Reformat this chapter to include general principles regarding dose-response  
3 models (including general information from Appendix G after expert statistical  
4 review);
- 5 • Include a discussion of the future use of animal models;
- 6 • Bolster the discussion about human health outcomes in a separate chapter,  
7 including a discussion about susceptible populations and removing the discussion  
8 about quality of life;

9  
10 Some committee members suggested that the detailed discussions of the dose-response  
11 models from this chapter and Appendix G could be included in a second more advanced MRA  
12 document and/or separate white papers. However, overall, the committee believed strongly that  
13 this current document should be published quickly as an MRA overview, with revisions directed  
14 toward improving scientific accuracy and clarity. This document could become an excellent  
15 reference book for MRA.

16  
17 As a comprehensive document, it makes sense to place many of the appendices back into  
18 the text of the appropriate chapters. The DWC recommends placing Appendix A into the text in  
19 the appropriate chapter; making Appendix B a separate chapter in the front or close to the front  
20 of the document as a separate chapter; placing Appendix D toward the beginning of the  
21 document to illustrate general risk principles as a separate chapter; placing Appendix E at the  
22 end of one of the chapters as a concluding section in that chapter; and placing Appendix F at the  
23 end of the appropriate chapter.

24  
25 *Risk Characterization Chapter*

26 The clarity and utility of the Risk Characterization chapter could be improved in several  
27 ways by connecting this chapter to the previous ones. It would be helpful to have summaries at  
28 the ends of the Exposure chapter and Human Health Effects chapter about what pieces of  
29 information need to be brought forward from those respective chapters and folded into a risk  
30 characterization. Then, at the beginning of the Risk Characterization chapter, it would be helpful

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1 to summarize the elements that need to be drawn from the earlier chapters and incorporated into  
2 a risk characterization. This section should explicitly refer back to the Planning & Scoping and  
3 Problem Formulation chapter. The discussion of dose-response models in the Human Health  
4 Effects chapter and the Risk Characterization chapter is confusing, and it is not clear which  
5 framework and models should be used to reflect different aspects of the risk assessment. The  
6 uncertainty, variability, and sensitivity analysis section of this chapter is good and does not omit  
7 any significant approaches or methods. To improve the chapter, the Committee recommends the  
8 following:

- 9           • Explicitly refer back to the Planning & Scoping and Problem Formulation  
10           chapter;
- 11           • Include summaries at the ends of Chapters 3 and 4 about what pieces of  
12           information need to be brought forward from those chapters and folded into the  
13           risk characterization;
- 14           • At the beginning of Chapter 5, summarize the elements that need to be drawn  
15           from the earlier chapters and incorporated into the risk characterization;
- 16           • Trim unnecessary details and redundancy about the models in this chapter;
- 17           • Explicitly clarify the different models in each of the various aspects and  
18           applications of the risk assessment.

19

1 **INTRODUCTION**

2

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

7

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

23

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

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1 applications, flow diagrams for various types of assessments, and general considerations for  
2 conducting MRAs.

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

11  
12 The SAB was asked to provide recommendations in the following areas: how to improve  
13 the overall approach, the applicability of the protocol, the reasonableness of the protocol, the  
14 clarity of the protocol, the completeness and robustness of the protocol, and the ease of use of the  
15 protocol for conducting water-based microbial risk assessments. This task was posed to the  
16 Committee in the form of specific charge questions detailed below.

17  
18 The Committee deliberated on the charge questions during their September 21-22, 2009  
19 face-to-face meeting. Originally the charge question pertaining to Overarching Considerations  
20 was the last charge question, but the Committee felt that it was more appropriate as the first  
21 charge question, which is reflected below. The responses that follow represent the views of the  
22 Committee.

23

24 **RESPONSE TO CHARGE QUESTIONS**

25 **1. Charge Question 1 – Overarching Considerations**

26 **EPA's Office of Water, Office of Science and Technology (OST) would like this**  
27 **Protocol to provide a comprehensive and robust suite of approaches, tools, methods,**  
28 **and procedures to meet EPA's overall needs in preparing for, and conducting**  
29 **typical MRAs. OST would also like the Protocol to be informative, easy to use and**

1           **understand, and useful to outside stakeholders (states, communities, utilities,**  
2           **industry, and impacted parties).**

3  
4           **Please comment on the following:**

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

11   **1.1     Utility of the Protocol for Meeting EPA’s Overall Needs, Particularly the**  
12   **Comprehensiveness and Robustness of the Protocol**

13  
14           The Committee believes that the MRA Protocol is a valuable document that should be  
15 finalized quickly. However, this document is not really a protocol; that is, it does not lay out a  
16 step-by-step procedure for performing a microbial risk assessment. Rather, this document is an  
17 informative overview of the MRA process, describing the components of an MRA and  
18 delineating the data needs and possible models that could be used.

19  
20           The document is quite comprehensive in terms of addressing the topic of microbial risk  
21 assessment at an introductory level, and the Committee did not identify major information gaps.  
22 The chapters are well organized but additional editing is needed to improve the flow of  
23 information, particularly in the use of topic sentences to introduce forth-coming ideas and  
24 provide transition between paragraphs and sections. The document reads much like a textbook  
25 and, in this respect, it is helpful and convenient to have all information on MRA readily available  
26 in one location. This document is very useful and could be one of the main resources on MRAs  
27 in the future.

- 28           • To make the document more comprehensive and robust, EPA should add a few  
29           examples of MRAs conducted on microbial pathogens.

1 The chapters introduce the readers to the various components of MRAs, whereas the  
2 Appendices go into greater detail with figures, tables and frameworks in each area. The  
3 discussion on the roles of the risk assessors and the risk managers is good and clearly delineates  
4 these roles. Some attempts should be made to condense the writing of the document to make it  
5 more concise, without sacrificing the clarity in the document. This can be done by eliminating  
6 the wordiness of the document in various sections and removing material which is not central to  
7 the discussion (alternatively, this material could be better integrated in the document with the  
8 help of a skillful technical editor.)  
9

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

- 16 • It is recommended that a more advanced document on MRA be developed in the near  
17 future by EPA. One could then progress from an Introduction to MRA (this  
18 document) to advanced topics in MRA to actual MRAs on specific microbes; the  
19 actual protocol would be the second document and would lay out step by step  
20 procedures on how to conduct MRAs. Nevertheless, this document is excellent as a  
21 text on MRAs.  
22

## 23 **1.2 Flow and Continuity Within and Between Chapters** 24

25 The flow and continuity within all sections – the Executive Summary and  
26 Chapters 1-5 – are good but need to be improved. All of the chapters and the Executive  
27 Summary are well-written and informative. They are verbose in certain sections, however, and  
28 some condensation is warranted. The flow between the Problem Formulation, Exposure, Human  
29 Health Effects, and Risk Characterization chapters could be improved through the use of

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1 additional flow diagrams. Most of the Appendices are excellent, and add a wealth of detail to the  
2 document.

- 3       • It is recommended that a senior technical analyst with statistical expertise review  
4 Appendix G in particular, for accuracy in its description of the extant literature and  
5 methods, and to insure appropriate continuity between the discussions of the various  
6 statistical techniques discussed.

7  
8       During the previous internal and external reviews, it appears that there was some  
9 disagreement and changes made regarding what should be in the text and what should be in the  
10 appendices. Collectively, the DWC thinks that the general principles and information from the  
11 appendices should be moved into the body of the text. One of the options to consider is that the  
12 Agency could quickly produce (with good editing) this current MRA document as an introduction  
13 to MRA, while keeping the advanced and detailed discussions for inclusion in a second, more  
14 advanced MRA document and/or set of technical white papers.

15  
16       However, the majority of the DWC believes that this current MRA document should be  
17 kept as a comprehensive introduction to MRA. Suggestions from the DWC members that would  
18 improve the flow and while producing this as an overview of or introduction to MRA include:  
19 placing Appendix A back into the text in the appropriate chapter; making Appendix B a separate  
20 chapter in the front or close to the front of the document as a separate chapter; placing Appendix  
21 D toward the beginning of the document to illustrate general risk principles as a separate chapter;  
22 placing Appendix E at the end of one of the chapters as a concluding section in that chapter;  
23 placing Appendix F at the end of the appropriate chapter. Appendix G should be removed from  
24 the Appendix and placed into the document as a separate chapter, but as mentioned above and in  
25 the discussion below regarding charge question #4, technical statistical review would be  
26 required.

27 **1.3 Ease of Use and Utility for Outside Stakeholders**

28  
29       There was a good deal of discussion regarding the identities of the document's intended  
30 audience and the primary stakeholders. The DWC concluded that this document was meant to

1 first serve the scientists within the Agency and the groups they work with who may take on  
2 MRAs, and that the secondary audience and stakeholders would be the water industry. This  
3 document should be useful for these outside stakeholders as a primer for the scientist who is new  
4 to the field and wishes to understand the EPA's MRA process. The stakeholders and scientists  
5 new to this area should be able to read the main chapters and understand them.

6 **1.4 Changes or Enhancement to the Protocol to Ensure That it Meets the Needs of EPA**  
7 **and Outside Stakeholders**

8  
9 The strength of the document, explaining the principles of MRA, may also be its  
10 weakness **if the document is intended to be a protocol**. The emphasis of the current document  
11 appears to be more on understanding MRA than in implementing an MRA. This focus is  
12 apparent in comparing Chapters 2 and 4. Chapter 2 has a sense of direction and describes a  
13 process of implementation with specific step-by-step instructions on how to formulate problem  
14 to be addressed by MRA, and how to develop a suitable conceptual model. In contrast, Chapter  
15 4 is much more explanatory; the reader is not given directions, for example, on how to assess and  
16 choose dose-response models. One idea for resolving this tradeoff of too much direction without  
17 enough explanation or vice versa, is to develop a step-by-step protocol located in the beginning  
18 of the document. If the reader needs further understanding, the Committee recommends having  
19 the steps linked to expanded explanations in the body of the text. The protocol could follow the  
20 organization and format of other EPA protocols, such as Method 1623. Alternatively, general  
21 protocol steps for an MRA could be located in the introduction and detailed steps and  
22 explanations located in the body of the text. It may help to create an overall visual schema, using  
23 a flow chart or decision tree, of the overall MRA process at the beginning of the document. This  
24 approach is used in an abbreviated fashion in Appendix D with Text boxes D.1, D.2, and D.3. It  
25 may further help to provide in the introduction a thorough description of actual well-developed  
26 MRAs as examples to guide the reader, such as the MRAs performed by EPA in support of the  
27 development of both the *Surface Water Treatment Rule* and the *Long-Term Enhanced Surface*  
28 *Water Treatment Rule*.

29

30 Other enhancements to the document include the following:

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

10  
11 General principles from the Appendices should be captured into the appropriate chapters.  
12 Remaining detailed discussions from the chapters and appendices could be put into a second  
13 more advanced MRA document or in separate white papers. These changes would improve the  
14 flow of the information.

15  
16 With such modifications, this document could be entitled, *Introduction to Microbial Risk*  
17 *Assessment*. It could then be used in the same manner that the “Red Book” for carcinogenic risk  
18 assessment is used, as a foundation document for MRA.

19  
20 **2. Charge Question 2 – Planning & Scoping and Problem Formulation (Chapter 2)**  
21 **Please comment on the utility of this chapter to ensure that risk assessments are**  
22 **adequately conceptualized and planned appropriately to address risk management’s**  
23 **issues. Please provide any recommendations for enhancing the utility of this**  
24 **chapter.**

25  
26 **Please comment on any enhancements or expanded guidance needed to allow users**  
27 **to prepare and conduct risk assessments to address a broad range of types of types**  
28 **of risk management questions. Examples of types of EPA uses of MRA may be:**

- 29 a) **approaches to mitigation of environmentally-based microbial**  
30 **pathogen exposure risks;**

- 1           **b)     determination of acceptable health risks;**
- 2           **c)     identification of different exposure factors/routes;**
- 3           **d)     identification of microbial-based hazards in disease outbreaks;**
- 4           **e)     development and prioritization of research needs;**
- 5           **f)     competing risks ranking.**

6   **2.1     Utility of Chapter to Ensure that Risk Assessments are Adequately Conceptualized**  
7   **and Planned Appropriately**

8

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

19

20           The primary purpose of this document is to inform and guide EPA staff and its  
21 contractors in conducting MRAs. An important secondary purpose is to document for those  
22 outside the agency how these EPA assessments are done. In this regard, the document is quite  
23 successful; it describes the process thoroughly and helps a reader unfamiliar with the process to  
24 understand how an MRA is conducted and the types of information needed. The Agency’s goal  
25 of transparency is furthered by this type of document.

26   **2.2     Recommendations for Enhancing the Utility of the Chapter**

27

28           The word “protocol” generally implies a set of specific steps that must be taken. This  
29 MRA document is not really a protocol, but more of a framework or methodological approach.

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1 It provides a broad overview of how the assessments are done, with some good examples of what  
2 to include and how to proceed.

- 3       • The title of the document should be changed to eliminate the suggestion that this  
4 is a detailed, step-by-step process.

5  
6       This chapter contains a good collection of common definitions that are unique to this  
7 field. An “outsider” to the MRA field might find this helpful in understanding the process. It  
8 would be beneficial to include some additional clarification to indicate when stakeholders should  
9 be consulted in the process, and whether the result of a planning/scoping and problem  
10 formulation exercise would be subject to external review.

11  
12       The chapter could be improved if the diagrams were changed. For example, EPA has a  
13 general logic-diagram format used in drinking water regulations that is very helpful. Starting at  
14 the top, one proceeds in a downward direction, following a particular arrow. If there is a  
15 decision (yes/no) this is shown as a diamond, with arrows leading away from the corners of the  
16 diamond depending on the outcome of the decision. If there is an iteration, the arrow is shown  
17 looping back around to the starting point. Most of the figures in this chapter do not follow the  
18 standard logic-diagram format and if they were changed to this format, this would help tie all the  
19 pieces together to get to the end product of planning/scoping and problem formulation.

20  
21       Recently published results on shower biofilms (Feazel, et al. 2009) raise questions about  
22 the extent to which an MRA can or should be extended to cover exposures that have not been  
23 considered previously or recognized as problems for water-borne pathogens. This also included  
24 pathogens such as *Legionella*. Incorporating “novel” routes and opportunistic pathogens may  
25 require new data for a number of variables, but ignoring these routes could result in unrealistic  
26 MRAs for some pathogens and some populations.

27 **3 Charge Question 3 – Exposure (Chapter 3)**

28       **Please comment on any additional exposure tools, methods, or approaches that**  
29 **should be included to ensure a robust approach to adequately determining the**  
30 **microbial occurrence and human exposure factors relevant to health risks from**

1        **water. This includes support for the estimation of the magnitude, frequency,**  
2        **duration, and also additional types of exposure to microbial pathogens by the water**  
3        **route, as well as the range of characteristics of the exposed population and their**  
4        **exposure profiles.**

5  
6        The Exposure chapter of the draft MRA protocol is a relatively short chapter in the  
7 overall document. The chapter has a good, concise discussion of the key issues related to  
8 exposure assessment and its role in the overall risk assessment. Points that are (properly)  
9 emphasized include the ideas that the life cycle and ecology of microorganisms are critical points  
10 for understanding the exposure pathways that ultimately lead to an exposure assessment. The  
11 current document also notes that the exposure duration and the population characteristics are  
12 important variables in assessing overall exposure. Overall, this chapter is concise, informative,  
13 and clearly written. However, unlike the detailed discussions in some of the other chapters, this  
14 section consists largely of generalities, which makes it useful as a chapter in an introductory  
15 MRA document. Exposure assessment is often very venue- and microbe-specific and here is  
16 where previous EPA MRA examples could be included, such as that performed on  
17 *Cryptosporidium* risk assessment. This example would illustrate the exposure issues that need to  
18 be considered as well as delineate the type of specificity and quantitative data that are needed.

### 19    **3.1    Additional Exposure Tools, Methods, and Approaches**

20

21        The layout of the entire document is based on the breakdown shown in Figure 7 (p. 32 in  
22 the draft document), entitled “Analysis Phase Microbial Risk Assessment for Pathogens.” This  
23 chapter is concerned with the bottom three boxes on the left side of that document, called  
24 “Occurrence, Exposure Analysis, and Exposure Profile”. The profile is the net result of all the  
25 work that precedes; it is the bottom line of the characterization of exposure. Despite its extreme  
26 importance to the MRA, the exposure profile is given inadequate treatment in this chapter,  
27 compared to the rest of the document. Uncertainty analysis reported in the literature on drinking  
28 water MRAs has shown that exposure assessment is the primary factor driving the distribution of  
29 risk outputs; thus it remains a very important aspect of the MRA. Two examples from the  
30 literature are cited and explained in some detail, but the reader is left to ascertain what

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1 constitutes an appropriate statement of the exposure profile and the significance of generating the  
2 exposure data. The examples would be much more valuable if the general principles were  
3 explained in more detail; this section is too “soft” to be particularly useful.  
4

5 Exposure assessment for water applications will likely be far more complex in the future  
6 than is portrayed in this chapter. Throughout the chapter, the focus seems to be on natural water  
7 systems, where the human exposure is likely to occur through swimming or other recreational  
8 activities, i.e., where there is direct contact with raw untreated water. The protocol is supposed  
9 to be useful for that situation, but it must also be flexible enough to include more complex  
10 situations, such as assessing the risks associated with drinking water, where human exposure to  
11 pathogens has been attenuated by environmental factors or water treatment. MRA in drinking  
12 water is far more complex than MRA in recreational settings because the drinking water passes  
13 through a number of barriers before the water reaches the consumer. The subject of drinking  
14 water and the presence of these barriers is not discussed in the MRA document.  
15

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

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1 techniques used in this work are applicable to evaluating human exposure to pathogens in  
2 drinking water in large water treatment plants with multiple unit processes.

3  
4       Aside from drinking water, the document does not include exposure assessments  
5 associated with the use of reclaimed wastewater, recycled water, and gray water. All of these are  
6 important sources of water that will be used to amend current water supplies and/or improve  
7 water efficiency. Although the USEPA does not have current national programs in these subject  
8 areas, state agencies, which have recycling programs have used MRAs in their development of  
9 public policy for water recycling and will use the USEPA's MRA document for this  
10 purpose. There is a body of published literature in the area of MRA that the Agency can cite,  
11 for use of recycled wastewater in agricultural irrigation, swimming, and landscape irrigation  
12 practices (Asano, et al. 1992; Soller, et. al. 2004). Because the terminology of reclaimed  
13 wastewater, recycled water, and gray water will be unfamiliar to many, these terms will need to  
14 be defined and explained in detail. Given the recent cross connection between a reclaimed  
15 wastewater irrigation line and potable water supply line in Coomara, Australia (this is not the  
16 first time; there have been cross connection incidents in California with recycled wastewater,  
17 none associated with a waterborne disease outbreak) this remains a route of exposure wherever  
18 water conservation occurs. The Agency may want to add a footnote on this regard.

19  
20       Another weakness of this chapter is that it focuses on endemic exposure risks and not  
21 episodic exposure risks. An exposure assessment in drinking water will need to consider all the  
22 events leading to exposure and account for the likelihood of those events to occur. Pathogens in  
23 treated water supplies are far more likely to occur episodically than otherwise because they occur  
24 with such a low frequency. A series of seasonal events (such as a rare storm event on a  
25 watershed) can lead to a significant change in raw source water quality. If this change is severe  
26 enough it can lead to the overload and subsequent failure of a treatment system. However, the  
27 failure of water treatment systems is an extremely rare event because the events leading to it are  
28 not frequent and with adequate on-line real time monitoring are easily avoided. The low  
29 frequency of such failures needs to be captured and included in the drinking water exposure  
30 assessment.

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

9  
10 This chapter is the shortest of all the chapters, but the brevity is largely due to the  
11 omission of several important points. As noted above, the chapter does not include anything  
12 about the drinking water pathway as a possible exposure route for microbial risk; it is essential  
13 that this be addressed in all parts of the chapter. Another serious omission is a lack of discussion  
14 on the use of indicator organisms instead of direct measurements of pathogens. Indicator  
15 organisms or surrogates are used extensively in environmental risk management and provide  
16 many of the data sets on sources, transport and fate, as in the analytical methods chapter of Haas,  
17 Rose, and Gerba (1999). This discussion should start with the four characteristics of a good  
18 microbial surrogate as referenced in Kay and Fricker (1997). The discussion should then evolve  
19 to explain how the choice of using indicator organisms contributes to the uncertainty. Situations  
20 in which indicator organisms are more or less likely to be present than the true pathogens of  
21 concern should be addressed in this chapter.

22  
23 Other omissions should also be addressed. First, the lack of available data is a major  
24 limitation in assessing exposure, or the likelihood of exposure, in the development of any MRA.  
25 This problem should be highlighted to some degree, since it adds considerably to the uncertainty.  
26 Second, the chapter is missing a discussion of recently published MRAs that have been used to  
27 guide beach closures and recreational MRAs; a targeted literature search should reveal these  
28 sources. They do not have to be discussed in detail, but listing them, along with a brief  
29 description, would allow a reader to look them up for further detail. Third, the discussion  
30 regarding analytical methods and the interpretation of results needs to be expanded and given its

1 own section. Such a section would provide a better presentation regarding the interpretation of  
2 occurrence results, since different types of assays are used to enumerate pathogens. As noted  
3 earlier, the exposure assessment is the greatest source of uncertainty and the hazard assessment  
4 and critical control point analysis (HACCP) will probably point to the interpretation of the  
5 occurrence data as contributing the most to the overall uncertainty of the MRA. Some of these  
6 assays are designed only to detect and enumerate infectious pathogens, whereas others provide a  
7 response based on DNA or antigen (protein components) presence that does not differentiate  
8 between viable, infectious, and nonviable pathogens.

### 9 **3.2 Suggestions for Improvement**

10

11 The Committee's suggestions reflect the comments above about omissions and  
12 weaknesses. The early part of the chapter should emphasize not only the similarities but also the  
13 differences that exist between chemical, and microbial, exposure assessment. Exposure  
14 assessments for microbes can be substantially more challenging than it is for chemicals. The  
15 delineation of these differences will highlight the needs for data. If possible, giving specific  
16 suggestions about possible data sources, or how data might be obtained, for the performance of  
17 an MRA would be useful. A specific suggestion is that Appendix F, which is only one page in  
18 length, should be brought back into the chapter; it could be done as a "text box" if the authors  
19 think that it is disruptive to the overall flow. A more thorough discussion of what an "exposure  
20 profile" should include is essential for this chapter to be useful; the entire protocol emphasizes  
21 the central role that the exposure profile is to play in the overall risk assessment, and yet the  
22 section that describes that profile is weak. The example of recreational risk is used throughout  
23 the chapter, although its use could be improved in some places; of greater importance is to carry  
24 the example of microbial risks in drinking water throughout the chapter.

25

26 The discussion on exposure associated with methods is confusing and should be  
27 reorganized and further related to the other chapters (e.g., the dose-response chapter) is found in  
28 the discussion on page 45 under the heading "What is the Level of Pathogens in the Water  
29 Body?". The sentence that begins with "Assays used to quantify pathogens yield variable..."  
30 identifies three major points. These points relate to the analytical methods; the variable recovery

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1 rates associated with the assays; and the fact that the assays may not provide information on the  
2 viability of pathogens, which affects their ability to infect humans. While these are important  
3 points, their importance is lost in the subsequent discussion on evaluating the efficacy of  
4 treatment. The example of the oocyst excystation assay not providing information on the  
5 infectivity of the trophozoites is accurate from the standpoint of evaluating the effectiveness of  
6 UV as a treatment technology, but misses a larger point. If the assay used to enumerate the  
7 oocysts in the Dupont human infectivity study (1995) provides the same level of enumeration  
8 accuracy (with the associated limitations) as the excystation studies used to evaluate UV (early  
9 studies), then there should not be a relative difference between the two results. However, as the  
10 example points out, that is not the case, but what the discussion misses is that there may also be a  
11 change in the relative ratio of infective, viable, and nonviable oocysts in the sample between the  
12 source of the oocysts and the raw water intake. The human infective dose in developing the  
13 dose-response also carries with it uncertainty associated with the dose. Young, freshly harvested  
14 oocysts were used for the dose-response and are most often used for disinfection studies, yet  
15 when conducting environmental sampling, the age of the oocysts in any given sample can vary  
16 widely, as could the distribution of viable and infective oocysts. This difference leads to part of  
17 the uncertainty in the interpretation of the data, and thus certain assumptions need to be clearly  
18 stated and used in exposure assessment. When new methods are introduced, such as cell culture  
19 techniques to enumerate the number of infectious oocysts in water samples, they may allow  
20 refinement of the dose-response relationship (Slifko, et al. 1997; Slifko, et al. 1999; Slifko, et al.  
21 2002). This refinement can then be used to improve future exposure assessments.

22

23 The subsequent paragraph jumps to a discussion of how environmental factors can affect  
24 the numbers of microbes and spectrum of microbes. These analyses have the opposite problem  
25 from oocyst measurements, as culture techniques may underestimate the dose. These examples  
26 are based on assays for these bacteria based on the presence of viable organisms that can be  
27 cultured and grown, instead of relying on an examination of one stage in the life cycle of a  
28 protozoan (oocysts). It should be further pointed out to the reader that even the bacterial assays  
29 depend on the “state” of the bacteria to grow in the medium they are presented with in the assay

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1 (where and how do viable but noncultureable organisms fit into the interpretation of occurrence  
2 results for MRA?).

3

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

19

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

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

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

10 **4.1 Scientifically Accepted Dose-Response Models**

11

12 The discussion of scientifically accepted dose-response models in the chapter, when  
13 combined with Appendix G, was comprehensive and thorough. General principles from  
14 Appendix G are critical to interpreting the chapter and therefore should be merged into the  
15 chapter. Given the mathematical details and the DWC view that Appendix G needs very careful  
16 technical review and revision, the Agency could consider taking the remaining detailed  
17 discussions from this chapter and Appendix G and placing it into a second more advanced MRA  
18 document and/or separate white papers.

19

20 Consideration should be given to making the dose-response section a separate chapter  
21 from the description of the health effects. The data sets (feeding studies) and the mathematical  
22 approaches for addressing the dose-response models are quite distinct from the data sets and  
23 descriptions of health outcomes. Extrapolations to low dose always bring many uncertainties,  
24 because often, no data at the low doses is available. The dose-response data sets for bacteria  
25 often reflect this lack of data at low doses, whereas those for viruses and parasites usually do  
26 include low doses. The confidence levels surrounding the best-fit curve broaden with  
27 extrapolation to the low doses, and this concept should be included as one of the uncertainties  
28 surrounding the data. Furthermore, uncertainty is introduced when one extrapolates from  
29 information derived from a specific setting to the larger and more general circumstance. Take,  
30 for example, a specific study, which uses a specific experimental pathogen strain of microbe, and

1 examines the consequences in a defined and specific human group or population. When  
2 generalizing from this specific study the assumption may be made that this microbe was  
3 representative of all of the pathogenic strains of the microbe, and that the human population that  
4 was studied was representative of the entire human population. This may not be true, and the  
5 uncertainty introduced by this assumption should be mentioned.

## 6 **4.2 Animal Dose-Response Models**

7

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

14

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

29

1           The data are scanty for many human pathogens, especially considering the spectrum of  
2 health effects upon which a modeling exercise must rest. Considerable information relevant to  
3 some pathogens (*Cryptosporidium*, *E. coli*) is available, but little exists for many other pathogens.  
4 These scientific gaps will need to be filled.

### 5   **4.3   Human Health Outcomes**

6  
7           A better description of the human health outcomes associated with exposure to the wide  
8 range of environmental pathogens should be included in a very specific chapter devoted to this  
9 topic. A major observation was that this chapter contained little discussion of the health effects  
10 of interest and how mathematical approaches could be used to incorporate these effects into  
11 probability models or disease transmission models; the human health outcomes were not defined  
12 or delineated in sufficient detail. Responding to the two charge questions on mathematical  
13 modeling of health outcomes and animal or *in vitro* models could have been more vigorous had  
14 the health effects of interest been defined. The majority of the chapter focused on dose-response  
15 analysis, obviously an important topic, but did not define the health effects of interest *per se* to  
16 which modeling should be applied. For example, viral hepatitis may be a waterborne disease,  
17 but the word “hepatitis” is only mentioned in the entire document three times – once in a chart,  
18 once in an explanation that human hepatitis E is similar to the porcine variant; and once in a  
19 discussion of milder disease in children. The exposure models are elegant, but modeling must be  
20 grounded in factual data to have authenticity and to be useful to the reader of this document.

21  
22           In the section on human health effects, there is no mention of the spectrum of severity of  
23 health effects that may occur in a population. While the median health effect of some infections  
24 may be minor, some individuals - only some of whom may belong to a susceptible population -  
25 may suffer uncommon, yet severe effects. By way of illustration, most children with diarrhea in  
26 the US have mild illness, so the severity of the average or median case of diarrhea is minor.  
27 However, some children with diarrhea become dehydrated and require admission to hospital, and  
28 a small number of these children will die. Thus the spectrum of the severity of the illness is  
29 broad, ranging from subclinical infection to death, while the severity of the median case is of  
30 minor consequence.

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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 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.

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

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1 the modeling can be applied. The document could be improved by providing examples of the  
2 health effects of interest, and how they have been used in prior risk assessments to give the  
3 reader a sense of the literature. Were this suggestion to be followed, a response to the charge  
4 questions with more detail could be provided.

5  
6 The section in the Health Effects chapter that begins on page 56 is an admirable  
7 compendium of the mathematical models which have been, or could be, used to model the  
8 effects of fairly generic exposures in a population. These models address the extent or likelihood  
9 of a general health effect in the population, not the modeling of the specific human health effects  
10 of interest. Such information would then allow a more robust analysis of the models that may, or  
11 may not, exist for specific health effects. Table IV of the chapter, on pages 69-70, provides  
12 information on pathogens and models used to describe their effects. An additional column (or a  
13 separate table) should be included that delineates the anticipated health effects of these  
14 pathogens.

15  
16 A nexus of scientific advances is likely to substantially improve our understanding of the  
17 dose-response relationship between drinking water pathogens and human health outcomes in the  
18 near to mid-term future. These advances include:

- 19  
20
- The development and adoption of real-time pathogen detection in drinking water  
21 systems, spurred by homeland defense concerns;
  - The identification of specific genetic susceptibilities to microbial pathogens via  
22 rapid advances in genomic medicine; and
  - Improvements in surveillance systems which can better detect and follow human  
23 health syndromes, and specific disease, in the US population.
- 24  
25  
26

27 The first will allow us to understand the magnitude of, and variance in, waterborne  
28 microbial pathogen occurrence using novel technologies that bypass the limitations of current  
29 methods. Real-time molecular or chromatographic monitoring will undoubtedly reveal  
30 exposures that we would not otherwise be aware of. Our current system of episodic or

1 infrequent sampling, and detection via methods that depend upon pathogen growth, act as  
2 constraints in understanding the occurrence of pathogens.

3  
4 The second will identify specific susceptible populations beyond our current  
5 understanding. We currently recognize infants and children, the elderly or pregnant, and those  
6 immunocompromised by disease or drugs as susceptible to infectious agents. Genomic science  
7 is likely to identify specific genetic vulnerabilities to more microbial agents found in water, just  
8 as it is currently identifying the genetic basis for other infectious diseases such as Noroviruses,  
9 human immunodeficiency virus (HIV), severe acute respiratory syndrome (SARS), and Epstein-  
10 Bar virus (Lindesmith, et al. 2003). These advances will help us to understand the range of  
11 health effects in susceptible populations. The last advance will help us to understand population-  
12 wide health effects as well as effects in specific sentinel populations.

13  
14 In aggregate, improved occurrence data and improved outcomes information should lead  
15 to far more robust risk assessment.

#### 16 **4.4 Susceptible Populations**

17  
18 The chapter on Problem Formation includes a subsection on susceptible populations  
19 [“Initial host characterization” pages 38-40, section 2.3.2] that is closely related to this chapter  
20 on Health Effects; the authors should consider whether some or all of that subsection should be  
21 moved to, or concisely reiterated in, this chapter. Certainly different populations may be  
22 affected by different routes of exposure. The example is given of behavioral elements, such as  
23 the ingestion of raw sea food, which is the critical route of exposure for some diseases. However,  
24 much of the discussion about susceptible populations in this section is relevant to how diseases  
25 may be differentially expressed in susceptible populations. It is clear from the literature that  
26 certain populations including the elderly, immuno-compromised people, and young children are  
27 more susceptible to adverse outcomes (as seen with outbreaks of *E. coli* 0157: H7 and AIDs  
28 patients and *Cryptosporidium*). Currently there are no data that demonstrate that this  
29 susceptibility is a result of changes in dose-response functions. It appears likely that the  
30 increased susceptibility is related to an attenuated host response, once the infection has been

1 initiated. The dose relationship between infectivity and age (young and old)/immuno-  
2 compromised populations is ambiguous. There is a need to break down the host response into  
3 various components, including timing or onset of infection and disease severity. Such host  
4 response concepts have been acknowledged for food-borne bacterial infections (Buchanan, et al.  
5 2000) and need to be considered for the pathogen-host-environment interaction in MRA  
6 protocols.

#### 7 **4.5 Quality of Life**

8

9 The Committee does not believe that the quality of life discussion belongs in this  
10 document. Quality of life is not part of the risk assessment process, but rather part of the cost-  
11 benefit analysis. The Committee recommends removing this discussion from the document.

### 12 **5. Charge Question 5 – Risk Characterization (Chapter 5)**

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

#### 19 **5.1 Improvements to the Linkages between the Planning & Scoping and Problem** 20 **Formulation, Exposure, and Human Health Chapters**

21

22 This chapter is a good summary of risk characterization and of the models used in this  
23 area. It is written clearly and concisely. However, a number of improvements should be made to  
24 strengthen this important chapter. Firstly, it would be helpful to have summaries at the ends of  
25 Chapters 3 and 4 about what pieces of information need to be brought forward from those  
26 respective chapters and folded into a risk characterization. Then, at the beginning of Chapter 5,  
27 it would be helpful to summarize the elements that need to be drawn from the earlier chapters  
28 and incorporated into a risk characterization. Although these changes might seem simplistic or  
29 repetitive, they would help clarify the links between the components of the risk assessment and  
30 would improve the continuity of the document as a whole.

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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. It is necessary to do two things: (1) trim 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), and (2) clarify 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 Agency should think about the terms used to describe “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 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. Some of the topics that are in Appendix D

1 and that are not already addressed in Chapter 5 (i.e., the topics covered in Sections D.4-D.10)  
2 might be better placed, in overview/summary format, within Chapter 5.

## 3 **5.2 Uncertainty, Variability, and Sensitivity Analysis**

4

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

12

13 In any case, this document should acknowledge, and describe in an appropriate level of  
14 detail, the principles and practices regarding uncertainty, variability and sensitivity analysis  
15 presented in existing Agency documents that are, or could be, relevant to the conduct of MRAs.  
16 These include *Guiding Principles for Monte Carlo Analysis* (USEPA, 1997); *Report of the*  
17 *Workshop on Selecting Input Distributions for Probabilistic Assessments* (USEPA, 1999);  
18 *Guidelines for Preparing Economic Analyses* (USEPA, 2000a); *Using Probabilistic Methods to*  
19 *Enhance the Role of Risk Analysis in Decision-making with Case Study Examples* (External  
20 Review Draft) (USEPA, 2009). This latter document includes a case study on the *Two-*  
21 *dimensional Probabilistic Risk Analysis of Cryptosporidium in Public Water Supplies, with*  
22 *Bayesian Approaches to Uncertainty Analysis* which was conducted in support of the  
23 development of the *Long Term 2 Enhanced Surface Water Treatment Rule*. This case study  
24 could serve as one of the case examples that the Committee is recommending to be added to the  
25 revised document.

26

27 With the publication of so many guidelines, it would help to attain some degree of  
28 consistency in public policy if frameworks and approaches to risk assessment were consistent.  
29 This consistency could be achieved by referencing and using existing guidelines, noting  
30 exceptions or changes in the guidelines as dictated by legislative or executive direction.

1 Guidelines are rarely recalled or revised based on new science, so changes to previous guidance  
2 need to clearly and duly noted to improve the transparency of decision making within the agency.

3  
4 The uncertainty analysis can be done using a Monte Carlo approach to examine each  
5 element in the MRA to determine contributions to overall risk outputs. Those factors (for  
6 example in exposure assessment) that may be contributing to most of the uncertainty of the final  
7 result may pinpoint where more data are necessary or where risk management decisions should  
8 be focused in the development of policy. Applying the HACCP system which has been used in  
9 food safety could be useful as part of this activity, whereby the risk characterization could be tied  
10 to best management approaches.

### 11 **5.3 Other Recommendations**

12

13 Overall, the Committee felt that Chapter 5 could benefit from significant editing to better  
14 focus the chapter and to assure that the essential elements of the chapter are not lost in the  
15 tangential discussions and excessive detail. Specifically, the Committee recommends the  
16 following:

- 17 • Edit Section 5.1.1 on Historical Context (minimize the verbiage) with the  
18 exception of the last paragraph on EPA policy;
- 19 • Shorten Section 5.1.3 on Parsimony to one paragraph which defines the concept,  
20 and to state how to make the determination (drawing on the concepts outlined in  
21 Appendix G.1);
- 22 • Change Section 5.1.2 to be consistent with EPA's *Risk Characterization*  
23 *Handbook* (USEPA, 2000b). (Because the document we were asked to review is  
24 primarily a document for EPA use, the terminology for risk assessment, and  
25 particularly for Risk Characterization, should be consistent with EPA's risk  
26 assessment terminology. In some places in the document, the terminology  
27 appears to reflect the ILSI Framework for Microbial Risk Assessment rather than  
28 EPA's own risk assessment terminology. For example, EPA's Handbook does  
29 not define Risk Characterization as consisting of two major steps – risk estimation  
30 and risk description.)

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- 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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**1-12-10 Science Advisory Board (SAB) Drinking Water Committee Advisory Report**

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