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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 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 on: 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. The framework had been in development
3 for many years and has undergone extensive internal and external review. It is important for
4 EPA to complete this document as soon as possible. The key points and recommendations are
5 detailed in the report.

6
7 The Committee generally finds the document to be well-written and clear. However, the
8 document does not fulfill its intended purpose as a “protocol”. A protocol generally implies a set
9 of specific steps that would be undertaken to perform, in this case, an MRA. Rather than a
10 protocol, this document describes the framework, types of data and models and in general the
11 process and serves as a good introduction to MRA. Nevertheless, as a framework or an
12 introduction to MRA, the document does provide a useful consolidation of MRA information.
13 The Committee recommends: (a) adding more illustrative examples of actual EPA MRAs
14 throughout the document; (b) renaming the document as a Framework or Introduction to MRA;
15 (c) developing a more advanced MRA document that would provide a step-by-step process on
16 conducting MRAs in the near future.

17
18 The SAB appreciates the opportunity to provide EPA with advice on this important
19 subject. We look forward to receiving the Agency’s response.

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Sincerely,

Dr. Deborah L. Swackhamer, Chair
EPA Science Advisory Board

Dr. Joan Rose, Chair
SAB Drinking Water Committee

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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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**U.S. Environmental Protection Agency
Science Advisory Board
Drinking Water Committee**

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2 Evolutionary Biology, Director of the Joint Institute for Biological Sciences and Director of
3 the Center for Environmental Biotechnology, Oak Ridge National Laboratory, University of
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5
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16 CA

17
18 *not able to participate in this review
19

20
21
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ACRONYMS

CRA	Chemical Risk Assessment
DWC	Drinking Water Committee
EPA	Environmental Protection Agency
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
PS/PF	Planning/Scoping and Problem Formulation
SAB	Science Advisory Board

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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”.

7
8 Overall the Committee finds the document to be well-written and clear. However, the
9 Committee does not feel that the document fulfills its intended purpose as a protocol. A protocol
10 generally implies a set of specific steps that must be taken. Rather than a protocol, the
11 Committee feels that this document is more of a framework and an introduction to MRA.
12 Nevertheless, as a framework or introduction to MRA, the document does provide a useful
13 consolidation of MRA information. The Committee recommends:

- 14 • Adding more examples of actual MRAs throughout the document;
- 15 • Renaming the document as a Framework or Introduction to MRA rather than a
16 Protocol;
- 17 • Developing a more advanced MRA document that would provide a step-by-step
18 process for conducting MRAs in the near future.

19
20 With regards to the specific charge questions relating to each of the chapters, the
21 Committee finds that the Planning/Scoping and Problem Formulation chapter is generally useful,
22 but that it is missing sufficient detail, such as flow charts, figures, and logic trees that would help
23 tie all the pieces together to get to the end product of planning/scoping and problem formulation.

- 24 • The Committee recommends formatting all the diagrams in the chapter to the
25 standard logic-diagram format.

26
27 The Exposure chapter provides a good, concise discussion of the key issues related to
28 exposure assessment and its role in the overall risk assessment; however a few weaknesses and
29 omissions were identified. The exposure profile section of this chapter is the sum result of
30 exposure characterization, yet is not given adequate treatment in this chapter and is not

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1 comprehensive enough, given that sensitivity analyses have shown that the greatest variability to
2 risk assessment is the exposure. The chapter focuses on endemic exposures rather than episodic
3 exposures, which are more likely to occur with pathogens in treated water. The chapter seems to
4 focus more on risks from recreational exposure as opposed to risks from drinking water exposure
5 and drinking water examples should be used throughout, including unusual routes associated
6 with biofilms and inhalation. The subject of indicator organisms instead of direct measurements
7 of pathogens is not discussed and should be added. Indicator organisms are used extensively in
8 environmental risk management and may provide the most rich data base on some of the
9 exposure issues associated with sources, transport and fate. The uncertainty associated with such
10 choices, and situations in which indicator organisms are more or less likely to be present than the
11 true pathogens of concern should be addressed in this chapter.

- 12 • The Committee recommends that the chapter include a more thorough discussion
13 of the exposure profile, episodic exposures, drinking water exposures, and the use
14 of indicators.

15

16 The Human Health chapter is largely devoted to dose-response models. The discussion
17 on dose-response models was fairly comprehensive and thorough, when combined with
18 Appendix G, but could be shortened to be more concise. It would be useful to include a
19 discussion of the gnotobiotic piglet as an animal dose response model. This model has been used
20 for many human enteric pathogens. Dose-response should be developed as a separate chapter.
21 Description of the data sets and uncertainty analysis is needed including extrapolation to low
22 doses (e.g. how the dose-response relationships uncertainty shifts at lower levels of exposure)
23 and adequacy of the experimental data considering microbial and host factors.

24

25 The Human Health chapter should be developed further. One major omission in this
26 chapter is the lack of discussion of human health outcomes from microbial pathogen exposure,
27 such as the types of illnesses, the severity of illness, and the specificity of syndromes. A
28 discussion about susceptible populations should also be included in this chapter because
29 susceptibility affects the expression of the disease in humans, e.g. the health effects. The

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1 Committee also does not feel that the quality of life discussion belongs in this chapter. Quality
2 of life is not part of the risk assessment process, but rather part of the cost-benefit analysis.

3 The Committee recommends:

- 4 • Combining Appendix G with the dose-response chapter and making the
5 discussion of dose-response models more concise; including a discussion of the
6 genotoxic piglet animal dose response model;
- 7 • Bolstering the discussion about human health outcomes in a separate chapter; and
8 removing the discussion about quality of life;
- 9 • Including a discussion about susceptible populations.

10

11 There are several ways to improve the clarity and utility of the risk characterization
12 chapter. It would be helpful to have summaries at the ends of the exposure and human health
13 chapters about what pieces of information need to be brought forward from those respective
14 chapters and folded into the Risk Characterization. Then at the beginning of the risk
15 characterization chapter, it would be helpful to summarize the elements that need to be drawn
16 from the earlier chapters and incorporated into the Risk Characterization. This should explicitly
17 refer back to the planning/scoping and problem formulation chapter. The discussion of dose-
18 response models in both the human health effects chapter and the risk characterization chapter is
19 confusing and it is not clear which framework and models should be used to reflect different
20 aspects of the risk assessment. The uncertainty, variability, and sensitivity analysis section of
21 this chapter is good and does not omit any significant approaches or methods. To improve the
22 chapter, the Committee recommends:

- 23 • Explicitly referring back to the planning/scoping and problem formulation
24 chapter;
- 25 • Including summaries at the ends of Chapters 3 and 4 about what pieces of
26 information need to be brought forward from those respective chapters and folded
27 into the Risk Characterization;
- 28 • At the beginning of Chapter 5, summarizing the elements that need to be drawn
29 from the earlier chapters and incorporated into the Risk Characterization;

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- 1 • Trimming unnecessary details and redundancy about the models in these chapters
- 2 (perhaps, capturing the detail in an appendix);
- 3 • Clarifying explicitly the different models in each of the various aspects and
- 4 applications of the risk assessment.
- 5

Comment [JBR1]: This does not reflect another recommendation made in the main text which says that all the appendices should be brought forward into the main document as chapters or incorporated into current chapters, so the committee should discuss this point.

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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 “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), in particular it has been used within the *Surface Water Treatment Rule* and the *Long-*
11 *Term Enhanced Surface Water Treatment Rule*. MRAs (although not formal quantitative MRAs)
12 have also partially supported the development of health-based ambient water quality criteria and
13 biosolids criteria under the Clean Water Act (CWA). These criteria have assisted in protecting
14 against potential adverse human health outcomes and exposures to infectious disease
15 microorganisms in recreational waters and land application of wastewater biosolids. OW
16 developed “the MRA Protocol” to provide Agency guidance for performing microbial risk
17 assessments. Current Agency risk assessment guidance is geared towards chemical risk
18 assessment, but MRAs do not fit completely within the chemical-risk framework because of
19 microbial and host factors that are specific to microbial risk assessments. The MRA Protocol
20 was developed to help risk assessors address these factors in a consistent manner.

21

22 General features of the MRA Protocol include 1) a modular component concept; 2)
23 flexibility to allow for unique Agency requirements which could be inserted or replace default
24 parameterization; 3) discussion of various risk assessment applications including for regulatory
25 purposes, outbreak investigation, identification and prioritization of research, investigation of
26 risk-risk trade-offs, emergency response, and mitigation; 4) consistency with a companion
27 document, the Thesaurus of Terms and Definitions in MRA and MRA terms and definitions for
28 the US and international agencies; and 5) development of appendices showing details on dose-
29 response modeling applications, flow diagrams for various types of assessments, and general
30 considerations for conducting MRAs.

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1 Specific features of the MRA Protocol include: 1) an expanded problem formulation
2 Chapter, with planning, scoping, and tiered conceptual modeling; 2) an Exposure Chapter, which
3 includes pathogen occurrence and exposure analysis; 3) a Health Effects Chapter, with dose-
4 response and health effects, dose response modeling applications, and dynamic population
5 susceptibility models; and 4) a Risk Characterization Chapter, which applies EPA's Risk
6 characterization handbook, invoking uncertainty, variability, comparisons to similar risks,
7 alternative approaches/solutions, and input to inform risk management decisions.

8
9 The SAB was asked to provide recommendations on: how to improve the overall
10 approach, the applicability of the protocol, the reasonableness of the protocol, the clarity of the
11 protocol, the completeness and robustness of the protocol, and the ease of use of the protocol for
12 conducting water-based microbial risk assessments.

13
14 The Committee deliberated on the charge questions during their September 21-22, 2009
15 face-to-face meeting. The charge to the Committee is presented below. Originally the charge
16 question pertaining to Overarching Considerations was the last charge question, but the
17 Committee felt that it was more appropriate as the first charge question, which is reflected below.
18 The responses that follow represent the views of the Committee.

19

20 **RESPONSE TO CHARGE QUESTIONS**

21 **1. Charge Question 1 - Overarching Considerations**
22 **OST would like this Protocol to provide a comprehensive and robust suite of**
23 **approaches, tools, methods, and procedures to meet EPA's overall needs in**
24 **preparing for, and conducting typical MRAs. OST would also like the Protocol to**
25 **be informative, easy to use and understand, and useful to outside stakeholders**
26 **(states, communities, utilities, industry, and impacted parties).**

27

28 **Please comment on the following:**

29 **a) utility of the Protocol for meeting EPA's overall needs, particularly on**
30 **the comprehensiveness and robustness of the Protocol;**

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- 1 **b) flow and continuity within and between chapters;**
- 2 **c) ease of use and utility for outside stakeholders;**
- 3 **d) any changes or enhancements to the Protocol to ensure it meets the**
- 4 **needs of EPA and outside stakeholders.**

5 **1.1 Utility of the Protocol for Meeting EPA’s Overall Needs, Particularly the**
6 **Comprehensiveness and Robustness of the Protocol**

7
8 In contrast to EPA’s documents on Chemical Risk Assessment, which are far more
9 advanced compared to MRA, this document is a good introduction to MRA. However, the
10 Committee was initially confused by the title expecting a very different type of document in
11 which a protocol could be used to perform an MRA. The document is informative and clearly
12 written as an overview and summary describing the components including data needs and
13 models used in an MRA. In terms of addressing the topic of microbial risk assessment at an
14 introductory level, the document is quite comprehensive and the Committee did not identify
15 major information gaps. The chapters are well organized and easy to read. The document reads
16 much like a textbook and in this respect it is helpful and convenient to have all information on
17 MRA readily available in one location. To make the document more comprehensive and robust,
18 EPA should add a few examples of MRAs conducted on a few microbial pathogens. The
19 chapters introduce the readers to the substance and generalities of MRA, whereas the Appendices
20 go into much greater detail and depth in each of the areas. The discussion on the roles of the risk
21 assessors and the risk managers is good and clearly delineates these roles. Some attempts should
22 be made to condense the writing of the document slightly (by approximately 10%) to make it
23 more concise, without sacrificing the excellent clarity in the document. This can be done simply
24 by eliminating the wordiness of the document in various sections.

25
26 This document should be very useful to professionals in and outside government who
27 conduct MRA, and to scientists who are new to the field of MRA and who want to learn about
28 this process. Some decision should be made on whether this document is really a Framework, a
29 Guidance, or an Introduction to Microbial Risk Assessment. This document is really more of an
30 introduction to Microbial Risk Assessment rather than a Protocol. It is recommended that a more

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1 advanced document on MRA be developed in the near future by EPA, with actual examples of
2 risk assessments. One could then progress from an Introduction to MRA (this document) to
3 advanced topics in MRA to actual MRAs on specific microbes, which would be very instructive
4 to the user of this document and help them learn how to conduct MRAs. This is an excellent
5 document overall.
6

7 **1.2 Flow and Continuity Within and Between Chapters**

8

9 The flow and continuity within all sections – the Executive Summary, and
10 Chapters 1-5, are good. All chapters and the Executive Summary are well-written, clearly
11 written, and informative. However, it is verbose in certain sections, and some condensation,
12 approximately 10%, in the overall text is warranted. The flow between the problem formulation,
13 exposure, health and risk characterization chapters could be improved by using more flow
14 diagrams. The Appendices are excellent and add a wealth of detail to the document. However,
15 some of them, particularly the last Appendix, should be made into actual separate chapters and
16 placed into the body of the document, or added to certain chapters. During the internal and
17 external reviews there was some disagreement and changes made about what should be in the
18 text and what should be in the appendices. However the DWC as a body reviewing the
19 document does represent a broad group of multidisciplinary scientists and as an introductory
20 document, the Committee feels that more from the appendices should be moved into the body of
21 the text as opposed to less.

22 **1.3 Ease of Use and Utility for Outside Stakeholders**

23

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

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1 **1.4 Changes or Enhancement to the Protocol to Ensure it Meets the Needs of EPA and**
2 **Outside Stakeholders**

3
4 The strength of the document, explaining the principles of MRA, may also be its
5 weakness IF the document is intended to be a protocol. The emphasis of the document appears
6 to be more on understanding MRA and less so in implementing an MRA. This is apparent in
7 comparing chapters 2 and 4. Chapter 2 has a tone of direction and a feeling of implementation
8 with specific step-by-step instructions on how to go about formulating the problem and
9 developing the conceptual model. In contrast, chapter 4 is much more explanatory; the reader is
10 not given directions, for example, in how to assess and choose dose-response models. One idea
11 for resolving this tradeoff of too much direction without enough explanation or vice versa, is to
12 develop a step-by-step protocol located in the beginning of the document and if the reader needs
13 further understanding have the steps linked to expanded explanations in the body of the text.
14 The protocol could follow the organization and format of other EPA protocols, for example
15 Methods 1623. Alternatively, general protocol steps for an MRA could be located in the
16 introduction and detailed steps and explanations located in the text body. It may help to create
17 an overall visual schema, using a flow chart or decision tree, of the overall MRA process at the
18 beginning of the document. It may further help to provide in the introduction a thorough
19 description of actual MRAs as examples to guide the reader. The Office of Water (OW) has
20 performed microbial risk assessments (MRA) in support of new regulations for microbial
21 pathogens in drinking water under the Safe Drinking Water Act (SDWA), in particular it has
22 been used within the *Surface Water Treatment Rule* and the *Long-Term Enhanced Surface*
23 *Water Treatment Rule*. This approach is used in an abbreviated fashion in Appendix D with Text
24 boxes D.1, D.2, and D.3.

25
26 Other enhancements to the document include:

- 27 • Clearly specifying the target audience and if there is more than one audience,
28 clearly specifying how they might differ in using the document;
- 29 • Providing an index at the end of the document;
- 30 • Providing a more detailed description of the Monte Carlo method in the Risk
31 Characterization chapter;

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- Producing an appendix describing software or programming code for performing the risk characterization and the associated sensitivity and uncertainty analyses.

All the Appendices **should** be converted into chapters, or added to the appropriate chapter they are relevant to. This would improve the flow of the information. In particular:

- Appendix A, Flow Diagrams for Various Types of MRAs, can and should be placed into one of the chapters.
- Appendix B, Factors Unique to Microbial Risk Assessment as Compared to Chemical Risk Assessment, should be the second or third chapter in this document, since this Appendix details how MRA derives from Chemical Risk Assessment (CRA).
- Appendix C, Other Risk Frameworks That Are Consistent with the MRA Protocol Framework, is very short and can be placed into one of the chapters.
- Appendix D, MRA General Concepts, should be placed as a separate chapter in the text, right after the chapter that would be derived from Chapter B.
- Appendix E, Possible Future MRA Goals and Research Needs, should be made into the concluding chapter in the text that looks toward the future in the area of MRA.
- Appendix F, Exposure Analysis Annex, can be placed back into the chapter on Exposure Analysis.
- Appendix G, Human Health Effects Annex, is an excellent section and also should be taken out of the Appendix and placed into the body of the text after the Exposure Analysis chapter.

Comment [JBR2]: Do we want ALL the appendices converted and a new appendix produced??? As suggested but the bullet immediately above.

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.

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

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

11 **2.1 Utility of Chapter to Ensure that Risk Assessments are Adequately Conceptualized**
12 **and Planned Appropriately**
13

14 Overall, this chapter provides a high-level discussion of how to plan and conduct an
15 MRA. The structure described in this chapter, which involves formulating the problem and
16 scoping out the entire process is excellent. It is particularly important to very specifically write
17 down the questions that are being addressed and to develop a plan for addressing them. This
18 approach applies not only to the conduct of MRAs but also to nearly any technical investigation.
19 The overall approach is sound and logical. It is particularly helpful to acknowledge up front that
20 the conduct of an MRA is an iterative process. As the investigation/assessment proceeds, new
21 information may point the investigator in a different direction, and the overall plan will be
22 adjusted accordingly.
23

24 The primary purpose of this document is to guide EPA staff and its contractors in
25 conducting MRAs. An important secondary purpose is to document to those outside the agency
26 how these assessments are done. In this regard, the document is quite successful; it describes the
27 process thoroughly and helps a reader unfamiliar with the process understand how it is conducted.
28 The agency's goal of transparency is furthered by this type of document.

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2.2 Recommendations for Enhancing the Utility of the Chapter

The word “protocol” generally implies a set of specific steps that must be taken. This MRA document is not really a protocol, but more of a framework or methodological approach. It provides a broad overview of how the assessments are done, with some good examples of what to include and how to proceed. The title of the document should be changed to eliminate the suggestion that this is a detailed, step-by-step process.

This chapter contains a good collection of common definitions that are unique to this field. An “outsider” in the MRA field might find this helpful in understanding the process. It would be beneficial 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 are changed to this format, this would help tie all the pieces together to get to the end product of planning/scoping and problem formulation.

Recently published results on shower biofilms (Feazel et al, 2009, PNAS) 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.

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1 **3 Charge Question 3 – Exposure (Chapter 3)**
2 **Please comment on any additional exposure tools, methods, or approaches that**
3 **should be included to ensure a robust approach to adequately determining the**
4 **microbial occurrence and human exposure factors relevant to health risks from**
5 **water. This includes support for the estimation of the magnitude, frequency,**
6 **duration, and also additional types of exposure to microbial pathogens by the water**
7 **route, as well as the range of characteristics of the exposed population and their**
8 **exposure profiles.**

9
10 The Exposure chapter of the draft MRA protocol is a relatively short chapter in the
11 overall document. The proposed Protocol has a good, concise discussion of the key issues
12 related to exposure assessment and its role in the overall risk assessment. Points that are
13 (properly) emphasized include the ideas that the life cycle and ecology of microorganisms are
14 critical points of understanding in the assessment of exposure. The current document also notes
15 that the exposure duration and the population characteristics are important variables in assessing
16 overall exposure.

17 **3.1 Additional Exposure Tools, Methods, and Approaches**

18
19 The layout of the entire document is based on the breakdown shown in Figure 7 (p. 32 in
20 the draft document), entitled “Analysis Phase Microbial Risk Assessment for Pathogens.” This
21 chapter is concerned with the bottom three boxes on the left side of that document, called
22 “Occurrence, Exposure Analysis, and Exposure Profile”. The profile is the net result of all the
23 work that proceeds—the bottom line of the characterization of exposure—and yet it is given
24 inadequate treatment in this chapter. Uncertainty analysis from the literature in drinking water
25 MRAs has shown that exposure assessment is the primary factor driving the distribution of risk
26 outputs, thus it remains a very important aspect of the MRA. Two examples from the literature
27 are cited and explained in some detail, but the reader is left to ascertain what constitutes an
28 appropriate statement of the exposure profile and the significance of the generating the exposure
29 data. The examples would be much more valuable if the general principles were explained in
30 more detail; this section is too “soft” to be particularly useful.

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A second weakness of this chapter is that it focuses on endemic risk and not episodic risk. Pathogens in treated water supplies are far more likely to occur episodically than otherwise. Throughout the chapter, the focus seems to be on natural water systems, where the human exposure is likely to occur through swimming or other recreation. The protocol is supposed to be useful for that situation, but it must also be useful to assess the risks associated with drinking water, exposure to residuals from wastewater treatment plants, and other environmental concerns that come under the scrutiny of EPA. All of these risks are typically episodic. The chapter needs to address one or more of these situations directly, with drinking water being the most common and therefore the most important to include.

This chapter is the shortest of all the chapters, but this might be 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. A second serious omission is that the use of indicator organisms instead of direct measurements of pathogens is not discussed. Indicator organisms are used extensively in environmental risk management and provide much of the data sets on sources, transport and fate. The uncertainty associated with such choices, and 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.

Two other omissions should also be addressed. First, the lack of available data is a major limitation in assessing exposure, or the likelihood of exposure, in the development of any microbial risk assessment. This problem should be highlighted to some degree, since it adds to the uncertainty of virtually all microbial risk assessments. Second, the chapter is missing discussion of recently developed models for risk assessments that have been used to guide beach closures; a targeted literature search should reveal these sources. They do not have to be discussed in detail, but listing them with a brief description would allow a reader to look them up for further detail.

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1 **3.2 Suggestions for Improvement**
2

3 The Committee's suggestions reflect the comments above about omissions and
4 weaknesses. The early part of the chapter should emphasize the challenges in performing
5 exposure assessments for microbes that are not encountered when assessing chemical risks; these
6 differences will highlight the needs for data. If possible, giving specific suggestions about
7 possible data sources, or how data might be obtained, for the performance of a microbial risk
8 assessment would be useful. A specific suggestion is that Appendix F, which is only one page in
9 length, should be brought back into the chapter; it could be done as a "text box" if the authors
10 think that it is disruptive to the overall flow. A more thorough discussion of what an "exposure
11 profile" should include is essential for this chapter to be useful; the entire protocol emphasizes
12 the central role that the exposure profile is to play in the overall risk assessment, and yet the
13 section that describes that profile is weak. Finally, the example of recreational risk is used
14 throughout the chapter, although its use could be improved in some places; of greater importance
15 is to carry the example of microbial risks in drinking water throughout the chapter.

16 **4. Charge Question 4 - Human Health Effects (Chapter 4)**
17 **Please comment on any additional scientifically accepted dose response models**
18 **(including advanced and validated threshold, empirical, or mechanistic models)**
19 **which should be included as tools for determining human dose responses from**
20 **waterborne exposures via oral, inhalation, and dermal routes, especially for low**
21 **dose extrapolation. Please comment on whether any specific animal or in vitro dose**
22 **response protocols, models, and methods should be included in this Chapter. If so,**
23 **please describe their applications and limitations in establishing human dose**
24 **response curves.**

25 **4.1 Scientifically Accepted Dose Response Models**
26

27 The discussion of scientifically accepted dose-response models in the chapter, when
28 combined with Appendix G, was comprehensive and thorough. Appendix G is critical to
29 interpreting the chapter and therefore should be merged into the chapter.

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1 **4.2 Animal Dose Response Models**

2

3 Consideration should be given to making the dose-response section as a separate chapter
4 as the data sets (feeding studies) and the mathematical approaches for addressing the dose-
5 response models are quite distinct from the data sets and descriptions of health outcomes.
6 Extrapolations to low dose, increasing the confidence levels and uncertainties surrounding
7 various strains of microbes and the role of the host factors should be addressed here.

8

9 This chapter does not include a discussion of animal models such as the gnotobiotic
10 piglet model which has been used for a number of human enteric (diarrheal) pathogens such as
11 many of the *Escherichia coli* groups which cause different forms of human disease; or of this
12 model in studying *Campylobacter jejuni*, *Salmonella*, *Cryptosporidium*, *Isospora*, or
13 *Helicobacter pylori*. Gnotobiotic piglets have also been used to study a spectrum of rotavirus
14 and even Norovirus isolates. The application of this specific model is dependent upon the
15 pathogen, and the health outcome of interest.

16

17 For many human pathogens, there is relatively scanty data for many pathogens, and for
18 the spectrum of health effects upon which a modeling exercise must rest. Thus, while there is
19 information relevant to some pathogens (*Cryptosporidium*, *E. coli*) there is little information for
20 many other pathogens.

21 **4.3 Human Health Outcomes**

22

23 A better description of the human health outcomes associated with exposure to the wide
24 range of environmental pathogens should be included in a very specific chapter devoted to this
25 topic. A major observation was that in the Health Effects section, there was very little
26 information and discussion the health effects of interest and how mathematical approaches could
27 be used to incorporate this into probability models or disease transmission models - in large part
28 because the outcomes of interest, e.g. the human health outcomes, were not defined or delineated
29 in sufficient detail. Responding to the two charge questions on mathematical modeling of health
30 outcomes and animal or in-vitro models could have been more vigorous had the health effects of

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1 interest been defined. The majority of the chapter focused on dose-response analysis, obviously
2 an important topic, but did not define the health effects of interest per se to which modeling
3 should be applied. For example, viral hepatitis may be a waterborne disease, but the word
4 "hepatitis" is only mentioned in the entire document three times - once in a chart, once in an
5 explanation that human hepatitis E is similar to the porcine variant; and once in a discussion of
6 milder disease in children. The exposure models are elegant, but modeling must be grounded in
7 factual data to have authenticity and to be useful to the reader of this document.

8
9 The first section of the chapter on health effects (4.1) mentioned a number of health
10 effects 'elements' that should be considered during risk assessment. These included duration and
11 severity of illness; the morbidity and mortality and long-term health effects; transmission to
12 others; and quality of life. These are described in a bit more detail over a 2-page section before
13 the dose-response analysis overview (4.2) begins.

14
15 The section on health effects does not include a description of some of the major health
16 syndromes such as watery diarrhea, nausea and vomiting, disseminated viral illness which
17 produces an influenza-like illness, dysentery, hepatitis, meningoencephalitis, etc. There is some
18 inkling of these as the subheading that describes chronic sequelae (4.1.3) lists some of the
19 delayed effects of infection. However, there is no corresponding section on the acute effects, and
20 the list of chronic effects is illustrative, not comprehensive. With such delineation, it may be
21 easier to identify where models, based in sound science, exist and where they do not.

22
23 Earlier in the document, in section 2.2.4 (page 24) on the Scope of problem formation,
24 the suggestions are made that the scope should include "Which infectious disease hazard is being
25 addressed; ...which human populations will be included in the risk assessment; ...and what health
26 outcome or endpoints are addressed by the risk assessment, including how the health outcome is
27 measured." After this the point is made that the scope of the assessment (infection, disease
28 symptom/s, mortality) must be defined. These are all health effects to which the modeling can
29 be applied. The document could be improved by providing examples of the health effects of
30 interest, and how they have been used in prior risk assessments to give the reader a sense of the

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1 literature. Were this to be done, a response to the charge questions with more detail could be
2 provided.

3
4 The section in the Health Effects chapter which begins on page 56 is an admirable
5 compendium of the mathematical models which have been, or could be, used to model the
6 effects of fairly generic exposures in a population. These address the extent or likelihood of a
7 general health effect in the population, not the modeling of the specific human health effects of
8 interest. Such information would then allow a more robust analysis of the models that may, or
9 may not, exist for specific health effects. Table IV of the chapter, on pages 69-70, provides
10 information on pathogens and models used to describe their effects. There is no column in this
11 table, nor is there an equivalent table, on anticipated health effects.

12 **4.4 Susceptible Populations**

13
14 In the chapter on Problem Formation there is a section ["Initial host characterization"
15 pages 38-40, section 2.3.2] on susceptible populations which may belong, in part, or should be
16 concisely repeated in this chapter on Health Effects. Certainly different populations may be
17 affected by different routes of exposure. The example is given of behavioral elements, such as
18 the ingestion of raw sea food, which is the critical route of exposure for some diseases. However,
19 much of the discussion about susceptible populations in this section affects the expression of the
20 disease in humans, e.g. the health effects. It is clear from the literature that certain populations
21 including the elderly, immunocompromised and young children are more susceptible to adverse
22 outcomes (as seen with outbreaks of *E.coli* 0157 H7 and AIDs patients and *Cryptosporidium*).
23 Currently there are no data that demonstrate that this change is a result of changes in dose-
24 response functions but are as a result of host response once the infection has taken off and
25 represent the range and distribution of types of symptoms and their severity.

26
27 and how the dose-response relationship is shifted to greater response at lower levels of exposure.

Comment [JBR3]: Not sure what this means, BUT I think I have addressed in 4.2

28 **4.5 Quality of Life**

29

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1 The Committee does not feel that the quality of life discussion belongs in this chapter.

2 Quality of life is not part of the risk assessment process, but rather part of the cost-benefit

3 analysis. The Committee recommends removing this discussion from the chapter.

4 **5. Charge Question 5 - Risk Characterization (Chapter 5)**

5 **Please comment on any improvements needed to achieve the necessary outputs or**

6 **linkages between the components of the problem formulation, exposure, and health**

7 **chapters to make risk characterization easier to conduct. Please comment on any**

8 **additional approaches or methods to address uncertainty, variability, and sensitivity**

9 **analysis of the various pathogen, health and exposure factors used in risk**

10 **characterization.**

11 **5.1 Improvements to the Linkages between the Planning/Scoping and Problem**

12 **Formulation, Exposure, and Human Health Chapters**

13

14 It would be helpful to have summaries at the ends of Chapters 3 and 4 about what pieces
15 of information need to be brought forward from those respective chapters and folded into the
16 Risk Characterization. Then at the beginning of Chapter 5, it would be helpful to summarize the
17 elements that need to be drawn from the earlier chapters and incorporated into the Risk
18 Characterization. Although this might seem simplistic or repetitive, it would really help with
19 clarifying the links between the components of the risk assessment, and would improve the
20 continuity of the document as a whole.

21

22 The discussion of models occurs both in Chapter 4 (relative to dose-response) and in
23 Chapter 5 (relative to risk characterization). This is somewhat confusing to the reader, since it is
24 not always clear if the same or different models may be applicable in each instance (i.e., does
25 one use the same tool(s) to model dose-response as one would to characterize uncertainty and
26 variability?). It also ends up being repetitive. It is necessary to do two things: (1) trim
27 unnecessary detail and redundancy about the models in these chapters (perhaps, capturing the
28 detail in an appendix), and (2) clarify explicitly the different roles that the (same or different?)
29 models play in each of these aspects of the risk assessment, to assure that the reader understands
30 what needs to be accomplished by the modeling exercise in each step.

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2 The Agency should think about the terms used to describe “static” vs. “dynamic”
3 modeling. These are not accepted terms used by the MRA field. Both approaches described can
4 be dynamic, however one approach takes into account the contagious nature of pathogens and
5 using disease transmission models as a part of the overall assessment (known as SIR, or
6 Susceptible, Infected, Recovery models) which are much more complicated with many more
7 assumptions and parameters needed to derive the risk output.

8
9 The chapter on Risk Characterization should also explicitly refer back to the problem
10 formulation, planning and scoping described in Chapter 2, especially in Sections 2.1 and 2.2. It
11 is important for the risk assessor to state at this stage whether, and how well the Statement of
12 Concern, and Statement of Purpose and Objectives that were identified up-front in the risk
13 assessment were, in fact, addressed. Although the topic of problem formulation is included as
14 one of the items that should be addressed in the risk description summary at the end of the
15 Chapter (Section 5.5), it should be given greater emphasis elsewhere in the Chapter as well.

16
17 The title of Appendix D - MRA General Concepts, is misleading. One would expect this
18 section to address principles and tools by which aspects of exposure, hazard and dose-response
19 assessment would be conducted. In fact, its entire focus is on Risk Characterization, but Chapter
20 5 never makes reference to its existence or content. Some of the topics not already addressed in
21 Chapter 5 might be better placed, in overview/summary format, within Chapter 5 (i.e., the topics
22 covered in Sections D.4-D.10).

23 **5.2 Uncertainty, Variability, and Sensitivity Analysis**

24
25 Uncertainty, variability, and sensitivity analysis are important and deserve emphasis in
26 this document. Section 5.4, which discusses these issues is good, and does not omit any
27 significant approaches or methods – which dataset drives the most variability and uncertainty in
28 risk estimation. No specific additional approaches or methods are recommended. The Agency
29 may choose to re-format this document such that the Chapters present general principles and the
30 Appendices present tool and process details. In this case, the detailed discussions of the

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1 uncertainty, variability and sensitivity analyses required for a credible and complete risk
2 characterization should be placed in appendices.

3 **5.3 Other Recommendations**

4

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

9

- Delete most of Section 5.1.1 on Historical Context, with the exception of the last paragraph on EPA policy.

10

11

- 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).

12

13

14

- Change Section 5.1.2 to be consistent with EPA's Risk Characterization Handbook (2000). Because this 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 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.

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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).

23

24

25

- 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.

26

27

- Remove the excessive detail on the models, such as Table 6, and Figure 12.

28

29

- Move or shorten Section 5.2.3 to an appendix. 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.

30