Pre-Meeting Preliminary Comments from the
EPA Science Advisory Board Drinking Water Committee
on EPA's *Draft Protocol for Microbial Risk Assessment to Support Human Health Protection for Water-Based Media*
as of September 17, 2009

Comments from Dr. David Sedlak , Submitted September 16, 2009

Summary:
The draft document, "Protocol for Microbial Risk Assessment to Support Human Health Protection for Water-Based Media" summarizes current approaches for conducting microbial risk assessment (MRA) for water. It appears to be derived from prior efforts by the NRC and other organizations that have developed MRA protocols. In its current form, the main audience for the document will be EPA staff members who are already familiar with MRA procedures (and who have probably read the NRC reports already). In my opinion, outside stakeholders who are not already well versed in MRA are unlikely to find the document to be very useful because it tends to focus on somewhat arcane topics and provides details without a lot of context to how they will be applied in practice. If the intent of the EPA is to make the document more accessible, it would be useful to include a few examples of typical applications of MRA for waterborne pathogens to illustrate how the MRA process is used and the types of issues that tend to be important.

Specific details:

Page 10: It is not clear what is meant by the term "wastewater use". Hopefully, the authors meant to say "wastewater reuse" or "water reclamation" which would be appropriate in these discussions.

MRA Protocol Framework (p. 10): I am uncertain where actual data on disease would be compared to predictions from risk assessment models. Would it help to mention such data here?

Page 32: Figure 7 is unclear and somewhat distracting. I don't understand how "Methods/Tools" which appears on both sides of the diagram fits in and don't see why the diamonds (indicating overlap) are needed.

In numerous places the document discusses the need for transparency to instill public confidence. Does the agency have a policy about putting risk assessment models on the internet so interested parties can try to replicate calculations?

I am uncertain of the intent of the long bullet point list that starts on the bottom of page 39. It seems like it is a list of issues that may be relevant to host characterization but it is unclear how risk assessors are supposed to use the information. It is also unclear if these are examples, the most important issues or a complete list of the issues that should be considered.

Page 46: The second paragraph discusses differences in pathogen concentrations in raw sewage based on health status and uses a comparison between the US and developing countries as an example of the differences. The main audience for this document is risk assessment scientists working in the US. Are there examples of large regional differences in the US or other developed countries? If not, maybe this is not an important source of variability.

Page 61, second paragraph: Risk assessors rely upon assumptions, not "belief".

Page 59, text box 7: It is unclear to me how the observation that filtration reduces the incidence of cholera is related to the dose-dependent nature of waterborne diseases.

Page 69, Table 4: The values of alpha and beta are shown to 3 or 4 significant figures. This seems to imply a lot more confidence in the data than what is probably merited. Also, a single value of the constants is provided in some cases in which three or four references are listed. Were the same values used in each reference?

Page 74: The last paragraph in 5.1.2 refers to a weight of evidence discussion. Should this be described in more detail somewhere in this chapter?

Comments from Dr. Jeffrey Griffiths , Submitted September 17, 2009

Introduction material

I don't see that the model includes effects upon households, eg. Lost wages or stigma because of an ill person in the household. (models on page 12, page 13). On page 22 there is some mention of this in terms of days of work lost. One may query what happens when an entire community has to turn to alternative water sources, or cannot work, or has some other community-wide modification. This goes to the issue of population analysis as also noted below.

In the example used which is of food borne transmission, there is use of a factor about what percentage is attributable to this route of transmission… yet these vary are in an epidemic the percentage is, by definition, changing, and vary by population, external temperature, refrigeration, cooking habits... hard to say that using a single metric reflects these factors.

In section 2.2.4., the populations involved are listed as the general population, special populations… the general population is composed of smaller sets of more or less susceptible individuals with varying degrees of susceptibility, genetic backgrounds, exposures… and health effects may not be a bell shaped curve! One may have several populations with radically different susceptibilities, or radically different responses to infection.

The Plan notes that the agency does not currently have 'acceptable' levels of exposure to micro-organisms. The 8 acute GI events per 1,000 fresh water exposures approaches 1%, and for marine waters is 19 per 1,000, nearly 2%, based upon assessments made over 20 years ago. These levels of risk would be unlikely to be considered acceptable now. The risk ranges noted on page 25 should be examined closely.

section 2.3.1, hazard identification. The definition of secondary spread on page 37 is open to debate re: completeness and in some circumstances may limit the risk assessment. Contamination of the environment from a primary source as well as direct person to person transmission both result in disease; perhaps direct secondary and indirect secondary transmission terms should be used. An example: some infections are spread both by person to person and also by person to object to person spread, but even if the latter is transitory, it may not be counted as secondary transmission. From a common sense point of view transmission from person A to persons B, C, and D would have been due to the infection in person A, whatever the mode of transmission, be it from direct contact or indirectly. The discussion on this matter follows the text on page 38.

The group of susceptible populations listed on page 38 does not include genetic background, which is becoming increasingly recognized as a root cause of susceptibility. It is mentioned on page 39, however, and so this may represent a minor inconsistency. By way of showing its relevance, for example, it appears that recent deaths in Australia due to H1N1 virus were overwhelmingly in people with immunoglobulin IgG2 subclass deficiencies, which are genetically determined. This information is based on abstracts being presented at the Infectious diseases meetings this week in abstract form ... in one study, 8/11 with such an IgG deficiency had died versus 2/13 without such a deficiency in another study; in another, 10/11 with severe

deficiency died with a IgG2 subclass deficiency vs 2/13 without the deficiency). Partial IgG deficiencies are common in some native American groups. In addition, obesity is now being examined as a risk factor, and the US population is increasingly obese.

In section 3.2.2, mention is made of the assumption that exposures are usually considered short term, e.g. in an epidemic setting for pathogens. There is substantial information that endemic exposure is important as well, and that ingestion of water may vary seasonally. This is discussed indirectly and mentioned as a major data gap at the end of section 3.2.4 on page 50. This may represent an important lacunae in the analytical framework.

Human Health Effects

In section 4.1.2, severity of illness is defined as the effects on the individual. The process then used is to essentially multiply this severity by the number of people estimated to have been affected, as handicapped by estimates of the severity in susceptible individuals. This approach may miss the effects on the larger community, e.g. health effects associated with the avoidance of water which is contaminated and the use of other sources of water which may or may not be "healthy." In general this point is made to bring up the issue of community-wide health effects for consideration.

Section 4.1.4, - secondary transmission - brief mention is made of the prior section discussing secondary spread on page 37 without further content. (See above comments)

Section 4.1.5 - discussion of Quality of Life.

The use of QALYs and DALYs is generally used for economic analysis and not risk assessment. As stated, there is "much controversy regarding the validity of these measures partially because there is no accepted "gold standard" for determining criterion validity." My concern is that this discussion may confused the readers (the audience) and suggest to them that these could or should be used in risk assessment.

Section 4.3, dose-response models

A note: a person can become infected, and transmit an infection, without being clinically ill. the factors mentioned on page 59 include threshold assumptions, which may differ for infection versus illness. Extrapolations made from epidemics and outbreaks usually utilize ill persons (not ill persons plus not-ill but infected persons) to obtain rough calculations of the extent of infection. In section 4.3.3. this is better discussed re; the use of Bayesian methods. this is represented in the model outlined on page 80, in the section on risk assessment and modelling.

A critical aspect of susceptibility, which affects dose-response models, is the assumption that prior exposure leads to some degree of immunity, or none. However, Moe et al have shown that having prior Norovirus infections with prior serum IgG reactive to Norovirus (as a secure marker of prior exposure) actually increases the likelihood of infection. The models for dose-response effects should explicitly note if this assumption of immunity after a prior infection has been

tested experimentally. On page 80, in the section on models, there is in fact the classic assumption of post-infection "protection from infection."

Threshold models have not been shown to be superior to the others mentioned on page 68 (exponential and Beta-Poisson) and thus the assumption of a threshold should be carefully examined when invoked. Also, these dose-response models are limited by the strains or genotypes tested of a pathogen, which may mislead us when predicting the effects of all strains or variants of a pathogen.

Comments from Dr. Gary King, Submitted September 17, 2009

Planning/Scoping and Problem Formulation (PSPF):

This chapter lays out in significant detail the process to following for the initiation of MRA. The level of detail in the text appears to provide potential informed users with a thorough overview of the planning and scoping process and the goals/functions and mechanics of problem formulation. Figures 5 and 7 give a broad overview of the general elements and flow of PSPF, but these should be supplemented with additional graphics that create a visual representation of the process and important decision points as well as entry points for key data/feedback/review.

The text might also clarify the triggers for implementation of quantitative versus qualitative assessments. How is this decision made? Are there specific guidelines, or is this somewhat ad hoc and too dependent on circumstances to specify?

Some additional clarification should also be added to indicate when stakeholders would be consulted in the process, and whether the result of a PSPF exercise would be subject to external review.

A "workflow" diagram and/or decision tree might be especially informative to many within and external to EPA, who are not specifically familiar with MRA details.

As a minor detail, the URL's in Table 2 did not lead to the resources specified. This should be rectified. Are there additional URL's that could improve access to tools by EPA and non-EPA users?

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

Comments from Dr. Richard Sakaji, Submitted September 17, 2009

Microbial Risk Assessment Protocol

General Comments:

"…provides a systematic approach for framing information to be considered, an outline for conducting and documenting risk assessment…"

"…developed as guidance…"

"…provide guidance to risk assessors and scientists; summarize MRA methods and techniques; …'

Due to the range of "water" applications (beach standards, wastewater discharges, and drinking water standards) it was necessary for this document to be more general and to provide more guidance than specifics. So while it is written and organized well, it does not appear to provide a consistent level of detail leaving many facets of MRA up to the Agency's contractors. Hence, this document, as it stands, is more of a guidance or framework document than a protocol. A true protocol would provide the reader with step-by-step specific details on how to conduct an MRA, with guidance on how to handle the lack or scarcity of data. MRA for these different water applications is at different stages of development. One would not and should not expect the level of detail for all applications to be the same.

2. Exposure Chapter 3

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

The chapter does a good job characterizing the data elements needed for an exposure assessment while providing the reader with potential sources of information (Appendix F). The chapter also appropriately characterizes some of the sources of uncertainty and variability that determine the "representativeness" of the data, but the protocol needs to be clearer on how uncertainty, variability, and lack of data should be addressed for risk managers, recognizing that such guidance might be tied to laws and policies that are program specific. How the data is used is a critical issue since risk managers will use the results of the risk analysis to establish public policy. However, the protocol provides little guidance on how the data should be assembled and used in the conduct of an exposure assessment.

The Exposure chapter seems to simplify the route between the source and the exposed individual. This may be more of an appearance than fact because of the scant detail provided.

"Exposure through drinking water is limited to the area that the public water supply serves…"

As noted in the text, exposure is more complex than this statement implies. People travel to or through other water systems for work or vacations (roadside restaurants with their own water supply used in the preparation of food and beverages) being exposed to water from different sources receiving varying degrees of treatment. An acute threat in a roadside restaurant would seem minor because of such a short window of opportunity for exposure, but it needs to be considered in the context of how long the exposure might be present. If monitoring is infrequent (small water systems), as was noted in the rTCR comments, the exposure could be present for an extended period of time. The problem becomes more complex if secondary routes of infection are considered. To some degree the exposure scenario in larger water is no less complex because of the infrastructure set in place.

Larger utilities may have multiple source waters. These sources might be mixed prior to entry into the distribution system or each source might have its own entry point into the distribution system. Groundwater and surface waters may receive little or no treatment for pathogen control, others may receive extensive treatment.

Once treated the water enters the distribution system it can be immediately used by some consumers or stored in reservoirs to meet demand peaks. The operation of a distribution is very complex network of loops or pressure zones which may, for a variety of reasons, be hydraulically isolated from each other. Within these networks there are a myriad of activities (not all of which are under the control of the water utility) that can impact the microbiological quality of the water being delivered (utilities may be replacing mains, new businesses may be installing new plumbing for kitchens, homeowners may be remodeling bathrooms or kitchens, and in some cities there may be dual water systems (containing recycled wastewater)).

Although the protocol indicates that it is not suppose to be an exhaustive document when it comes to references and supporting documentation, the discussion on exposure would benefit from the inclusion of documents such as:

1. Liang et al (2006) CDC article on waterborne disease outbreaks.

2. National Research Council, National Academies Press, *Drinking Water Distribution Systems*, (2006).

3. Geldreich, E.F. *Microbial Quality of Water Supply in Distribution Systems*, Lewis Publishers, 1996).

These references would provide the reader with a better understanding of how complex the exposure scenario between the source and the target is for a microbiological risk assessment in drinking water.

One element in the exposure assessment that stands between the source and the target in drinking water and recreational use is the water treatment or wastewater treatment plant. How do

drinking water or wastewater treatment processes fit into the exposure assessment? While there are mentions of treatment process trains in the exposure chapter, there is no substantive discussion on how they fit into the exposure assessment. Since treatment processes are often the only barrier that stands between microbial pathogens and the human population, the exposure assessment should provide greater discussion on how treatment processes should be incorporated into the exposure assessment.

The exposure section contains references to treatment, but these references are relatively vague and do not provide the reader with any guidance on how the treatment processes should be incorporated into the exposure assessment. Especially when the pathogens must get past the treatment processes before they reach their target. As some of the text intimates, treatment processes do not provide a constant quality output. Fluctuations in product quality are the result of perturbations in a number of different variables; source material quality, inadequate maintenance, poor design, poor operational protocols, or a variety of other reasons.

In a properly designed, operated, and maintained system, this variability can be minimized (not eliminated) to prevent substandard product from being released. So how does one characterize the probability of a pathogen in the source water passing through a series of water treatment processes before the consumer drinks the water at the tap?
In drinking water, the use of multiple barriers has been an old long held concept used by sanitary engineers in the development of water resources. Historically the multiple barriers referred to a series of steps (source water protection, treatment, and distribution) employed to prevent pathogens from reaching consumers.

How does one enumerate the risk associated with a series of events that are either independent (each filter operates independently of the others) or dependent on each other (the coagulation and flocculation process (single basin) prepares the water for multiple filters)?

"Although treatment (physico-chemical) has a marked effect on oocysts concentrations (frequency distribution shifted by 4 logs), there is still a small probability of high concentrations of oocysts in treated water that is related to occasional reduced performance of the treatment plant."

This statement is true, but illustrates the need for the exposure assessment to include a discussion on redundancy and reliability when evaluating the treatment process train so the risk manager understands what is meant by the term "occasional."

"If wastewater treatment or control processes are not consistent, such as may occur during storm (combined sewer overflows and sanitary sewer overflows), there may be associated temporal fluctuations in pathogen levels."

While this statement serves to highlight an important issue, i.e., those events that can lead to temporal variations in pathogen wastewater concentrations, maybe it can be rephrased. Combined sewer overflows or sanitary sewer overflows from storm events are not inconsistencies in wastewater treatment or control processes (although wastewater is being collected and conveyed to a wastewater treatment plant). The fact that these events take place

may be the result of poor or antiquated design and/or maintenance of the sewer collection system. These events are not controllable, but they are, if one understands their service area and conveyance system, to some degree predictable. They may remain uncharacterized for numerous reasons.

Data

Data is the foundation on which any risk analysis is built. Data needs are present in several elements of the risk analysis, e.g. the exposure assessment, risk assessment, cost-benefit analysis, etc. The quality and quantity of data available shapes the degree of confidence one has on the outcome. Appendix F. lists SDWIS as a source of occurrence information. However, as was noted in the rTCR review, using SDWIS for the rTCR negotiations raised several issues with respect to the representativeness of the database. Attempts to extract information were frustrating. The data actually used did not include several major states. As the agency is involved in an ongoing effort to employ probabilistic methods to the risk analysis process (in an attempt to eliminate the single point estimates of risk currently in use) it should be noted that this effort will not be successful without representative data on which to establish distributions.

Analytical Methods

"Assays used to quantify pathogens yield variable recovery rates and may or may not include information about the viability of the pathogens or their infectivity to humans."

This information should be identified and understood before information from the assay is allowed to be used in any exposure assessment. Reference should be made to the EPA Microbiological Alternative Test Protocol Guidance (April 2004) for information on the analytical methods. While there is a great deal of criticism regarding this guidance, the AIP from the rTCR negotiations committed the agency to working with stakeholders to improve the process.

The TCRDSAC recommends that EPA engage stakeholders in a technical dialogue in its review of the Alternative Test Procedure (ATP) microbial protocol for TC/*E. coli* methods for drinking water to determine if the criteria for acceptance of methods are consistent with the intent and objectives of the TCR, considering such issues as sensitivity, specificity, matrix interference, false positive and false negative results, temperature, and holding time, particularly with respect to the occurrence of TC and *E. coli* in drinking water supplies.

The SAB recommends the agency move forward with their commitment to reviewing the ATP and revising it based on the outcome from the technical dialogue with stakeholders.

"…ultraviolet (UV) light irradiation was not an effective treatment option…"

While this example serves to illustrate how critical it is to understand the limitations of the analytical methodology, the example detracts from the focus, i.e., dealing with the impact of methodological limitations on determining the "level of Pathogens in the Water Body." Overall,

the discussion would benefit from an example illustrating how the limitations in the analytical methods might contribute to the uncertainty and variability in the occurrence database.

"Exposure is not limited to a pathogen specific context. It can also be defined in terms of water quality indicators…"

"…to specify clearly the conditions under which the correlation is expected to be valid."

While specifying the conditions under which a correlation is expected to valid is a laudable goal, this presupposes that such a correlation has been established. To my knowledge such a correlation has yet to be established. Given the issues with indicators and different tests, there needs to be some discussion regarding the interpretation of analytical results.

Comments from Dr. Joseph Landolph, Submitted September 17, 2009

Review of EPA's Draft Protocol for Microbial Risk Assessment to Support Human Health Protection for Water-Based Media

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Charge Question #5: Overarching Considerations

a) Utility of the Protocol for meeting EPA's overall needs, particularly on the comprehensiveness and robustness of the protocol

This is an excellent document. As one familiar with chemical risk assessment, this document appears to me to be an excellent introduction to microbial risk assessment. The document is overall very informative, very comprehensive, and is written very clearly. All the chapters introduce the readers to the substance and generalities of MRA. The Appendices go into much greater detail and depth in each of the areas. The discussion on the roles of the risk assessors and the risk managers is very good and clearly delineates these roles. This document should be very useful to professionals in and outside government who conduct MRA, and to scientists new to this area who want to learn about this process.

b) Flow and continuity within and between chapter.

The flow and continuity within all sections – the Executive Summary, and Chapters 1-5, is very good. All chapters and the Executive Summary are well-written and clearly written, and are informative. The Appendices are all excellent. They add a wealth of detail to the document. Some of them, particularly the last Appendix, should probably be made into a separate chapter and be placed into the body of the document.

The continuity between the chapters and appendices is very good, as is the continuity between the individual chapters.

c) Ease of use and utility for outside stakeholders

This document should be very useful and easy to use for outside stakeholders. It is well-written and clearly written, and hence it is very easy to read and understand. It is an excellent primer for the scientist who is new to this area and wished to become competent in MRA. The stakeholders can read the main chapters and easily understand them – chapters 1-4 and the Executive Summary. For those sophisticated scientists who want to go deeper into this material, the Appendices would be particularly interesting material for them to deepen and strengthen their knowledge. For the novice in this area, he/she can simply read the Executive Summary and Chapters 1-4, and leave the Appendices until they have learned enough so they have a basic foundation and want to acquire further knowledge.

d) Any changes or enhancement to the Protocol to ensure it merits the needs of EPA and outside stakeholders.

My personal belief is that the Appendices should be converted into chapters, or added to the appropriate chapter they are relevant to. Then, this MRA Protocol should be converted into a textbook, and sold on the open market. It contains a wealth of valuable information and will be useful to the novice and the expert in this area.

e) Other Specific Comments and Criticisms

Executive Summary

The Executive Summary is clear and appropriately concise, and it is a very good overall summary and roadmap to the entire document.

Chapter 1. Introduction

Chapter 1 is written clearly and is a good summary of why Microbial Risk Assessments (MRAs) are conducted. There is a good discussion of the two previous workshops that EPA held in this area, and a generalized framework for assessing the risks for human disease following exposure to pathogens. Figure 3 on a generalized framework for assessing the risks of human diseases following exposure to pathogens is very useful (adapted from ILSI, 2000. Figure 4 on elements of risk assessment and risk management, adapted from NRC, l983, is also useful. Table 1, listing the elements of microbial risk assessment, adapted form ILSI, 200, is again useful in the context of this MRA document.

Chapter 2. Planning and Scoping and Problem Formulation

In Chapter 2, there is good discussion of Planning and Scoping and Problem Formulation. Figure 5, the Enhanced Problem Formulation Process Diagram, is a concise and clear diagram to explain Problem Formulation, and it does this reasonably well. Figure 6, Example of an Over (Top-Tier) Conceptual Model, is very clear and helps to focus the discussion that follows. The discussion of the components in the conceptual model narrative, including toosl, data inventory, summary of assumption, sources of variability and uncertainty, factors and data not included, and

explanation of why, identified gaps in the knowledge base, environmental sampling strategies and analysis methods, and intervention action options, were all listed and concisely discussed.

The discussion of Initial Host Characterization was thorough but concise, and listed the usual sensitive receptors in the human population on page 38. The section on Environmental Justice is appropriately concise.

Chapter 3. Exposure.

This chapter covers all the basic of exposure and exposure assessment in general terms and then in more specific terms. It is written very clearly. The occurrence subsection of this chapter is written and comprehensive manner. This chapter will be very useful for novices in this area as an introduction, and also for more senior investigators to ensure that all aspects of exposure/exposure assessment are covered.

The section on Characteristics of Exposed Populations is very good and specifically covers the aspects of sensitive receptors. Overall, this chapter is concise, informative, and clearly written.

Chapter 4. Human Health Effects

This chapter describes human health effects relevant to the Microbial Risk Assessment process. The section on Duration of Illness is very interesting and very informative. In Table 3, six pathogens – Cryptosporidium parvum, Giardxia llamblia, Shigells spp., Campylobacteria jejuni, Eshcerichia coli O157:H7, and rotaviruses – are listed, along with their incubation periods. This is very useful information for both scientists inside EPA and also for outside stakeholders. Section 4.1.2 on Severity of Illness, is concise and clearly written. Section 4.1.233, Morbidity, Mortality, and Sequaelae clearly lays out the definitions for morbidity, mortality, and Days Adjusted Life Years (DALYs), and lists sequellae for pathogens. Some of these sequellae listed are: auto-immune diseases, such as: 1) reactive arthritis, associated with Chlamydia, Salmonella, Shigella, Yersinia, Brucella, Leptospira, Mycobacteria, Neisseia, Staphylococcus, and Streptococcus; 2) Guillian Barre Syndrome, associated with Campylobacter; 3) Type I diabetes, initiated or accelerated by Coxsackievirus B4; ulcers and stomach cancer, associated with Helicobacer; 4) failure to thrive, lactose intolerance, chronic joint pain (associated with Giardia; and 5) neurological effets, associated with poliovirus, echovirus, Coxsackievirus, Listeria, and botulinum toxin. This is a very strong and informative section.

Quality of Life, Section 4.1.5, describes the concept as quality-adjusted life years (QALY), which is numerical value for quality of life and translating that numerical to a monetary measure, as detailed by WHO in 2001. This section also discusses the difference between DALYs and QALYs, and notes that these are not objective measures and require a descriptive conceptualization of health states. These authors note that EPA has used QALYs and Morbidity Inclusive Life Years (MILYs) in the regulatory impact analysis for the Final Clean Air Interstate Rule (EPA, 2005). and the Long Term 2 Enhance Surface Water Treatment Rule (EPA, 2006a).

Sectcion 4.2, Dose-Response Analysis Overview, describes the processes involved in conducting risk assessments, and discusses dose-response analysis, which uses data from human clinical studies, epidemiological studies, animal studies, and/or outbreaks to develop a mathematical relationship between the intensity of exposure or amount of intake and the subsequent occurrence of disease or infection. There is a good discussion here that a number of factors need to be addressed in the derivation of dose-response models and estimation of their parameters for microbial risk assessment, including statistical models to analyze or quantify dose-response relationships, human dose-response data, animal dose-response data, and source and/or preparation of challenge material or inoculums. These authors note that there are factors that overlap with exposure analysis, including utilization of outbreak or intervention data, route of exposure or administration, and duration and multiplicity of exposure. There is a good discussion of how the mathematical form of the dose-response model may very with pathogen or strain, route of administration, distribution of host statuses, and other factors
There is also a very good discussion of how the comparison of murine response to Listeria monocytoegnes (based on feeding studies) to that of humans (based on epidemiological data) indicates that there is a factor of approximately one million difference in LD50 values between the two hosts. This is very useful information, and indicates the difficulty in extrapolating from rodents to humans in risk assessment. Other useful examples of intra-species and inter-species variations in risk to various pathogens, such as tularemia and plague, are also discussed. There is a further good discussion of how route of exposure or administration (oral, dermal, subcutaneous) and the source and preparation of the challenge material or inoculum, impact infectivity of a pathogen and host response. The authors also discuss other factors affecting the dose-response relationship, including the duration of exposure, the number of exposures, and the time between exposures. In text box 7, the authors discuss the dose-dependency of host-pathogen interactions and how this field has been only partially developed, although there is some useful data here.

The authors also discuss in section 4,3, an Overview of Common Dose-Response Model Forms for Pathogens. They discuss that the two most commonly used dose-response relations are the exponential and the beta-Poisson models, both of which are only valid when their underlying assumptions are met. Other two-parameter models that have been proposed for use in microbial risk assessment, including the log-normal, log-logistic, and extreme value models, are also discussed, as are three parameter models, including the Weibull gamma, exponential gamma, Weibull exponential, and the shifted Weibull model. The difficulties in using three parameter models is that they require data at four or more doses, which is usually not available for many microbial pathogens, and this is discussed in detail. Points that are important to address in order to promote transparency and clarity in a MRA are also listed and discussed.

The exponential model is discussed in detail, and two very good examples are provided, Cyrptosporidium Feeding Studies and Dose-Response and Host Immunity in relation to noravirus (Tables 8 and 9). The exponential model is described very clearly, and is used when 1) microorganisms are distributed in water randomly and thus, follow the Poisson distribution; 2) for infection to occur, at least one pathogen entity must survive within the host, and 3) the probability of infection in a person or animal model per ingested or inhaled is constant. In this model, there is no minimum infectious dose, as a non-xero risk is predicted with any non-zero dose. This mode assume that there is no a single organism is sufficient to cause infection, and

that the ingested organisms must pass through "multiple barriers" to survive long enough to cause disease. In such a case, Pr – 1- exp(-rl), where Pr = probability of an individual exhibiting the response specified by the dose-response parameter , and r is the dose-response parameter that is fit to the data. The response to exposure may be development of clinical symptoms and/or microbiological or immunological evidence that microbes have persisted or multiplied in the body. The authors have given a very short and concise description of the exponential model here.

In section 4.3.2, the authors describe the beta-Poisson Model. This model is based on similar assumptions to the exponential model, except that the third assumption (that the probability of infection per ingested organism is constant) is relaxed. Here, the probability of surviving and reaching a host site (r in the exponential model) is beta distributed. Therefore, the model contains two parameters , alpha and beta, of the beta distribution. The beta distribution fits best when there is variability in the host-pathogen interaction, diversity in the pathogen (multiple strains of pathogen), or both. The most commonly used approximation the beta-Poisson model is:
$Pr = 1-(1 + D/\beta)-\alpha$ Here, beta is the location parameter, and determines the inflection point of the dose-response curve, and alpha is the shape parameter governing the steepness of the dose-response curve. An excellent description and explanation of the significance of this model follows.

In section 4.3.3, the authors discuss Bayesian Models. In this model, uncertainty intervals for the parameters and the dose-response function can be calculated from the posterior distribution at credible intervals. Here, a 95% credible interval has a 95% probability of including the parameter value, given the data. These are very complicated models, and the authors briefly discuss them, and refer the reader to publications summarizing these models.

In section 4.4, there is an excellent summary of available dose-response relationships for waterborne pathogens. Table 4 is an excellent compilation/summary of these models. Some graphical illustrations of these models would be very helpful for the reader to help them understand these models.

Chapter 5. Risk Characterization

With reference to the l983 NRC publication entitled, Risk Assessment in the Federal Government: Managing the Process (the "Red Book), the NRC defined risk characterization as " …the process of estimating the incidence of health effects under the various conditions of human exposure described in exposure assessment." In l996, the NRC redefined risk characterization as, "a synthesis and summary of information about a potentially hazardous situation that addresses the needs and interests of decision makers and of interested and affected parties. Risk characterization is a prelude to decision making and depends on an iterative, analytic-deliberative process. EPA further referred to risk characterization as "the process of organizing, evaluating, and communicating information about the nature, strength of evidence and the likelihood of adverse health or ecological effects form particular exposures." The authors discuss the process of risk characterization in general terms, and the exposition is clear for the

reader. It would be useful is some actual examples could be given for serious human pathogens here.

The authors appropriately discuss risk characterization as consisting of two major steps – risk estimation and risk description. The concept of parsimony in modeling is discussed in section. 5.1.3, where the complexity of a model is contrasted to the complexity of biology. Static and dynamic models were discussed, as were MRA model forms under development – stochastic dynamic MRA Models, Individual-Based Models, Spatially-Structured Models, etc. This chapter is an excellent summary of risk characterization and of all the models used in this area. It is written clearly and concisely and should be very useful to the stakeholders outside EPA, as well as to new employees entering EPA or those changing fields within EPA.

Appendix B.

Appendix B has a very good discussion of factors unique to MRA as compared to Chemical Risk Assessment. These include microbial growth and death, detection methodologies, genetic diversity of pathogens, host immunity and susceptibility, dose-responses ranges being broad for pathogen, secondary transmission, and heterogeneous spatial and temporal distributions.

Appendix D. MRA General Concepts

This appendix contains a very useful discussion of the following topics: the iterative nature of risk assessment, transparency, clarity, consistency, and reasonableness; opinion; the risk assessment team; the roles of risk assessors and risk managers, risk communicators and stakeholders; peer review; risk perception; This chapter is very clear, and is an excellent introduction to the topic of risk assessment/risk management for the beginner in this area.

Appendix E. Possible Future MRA Goals and Research Needs

This appendix points out that more research and development is needed in the areas of Human Health Effects, where populations may be exposed to discrete vs. continuous dose and exposure. There is also a need for developing criteria for the use of animal models for derivation of dose-response models. In addition, it is important to determine whether threshold nor non-threshold dose-response models are most appropriate. It is also important to develop biologically-based mechanistic models; these are being developed but not yet available. The authors also point out that it is important to develop methods to investigate dose-response relationships for immuno-compromised and other more sensitive populations.

In the area of general research needs to improve MRA, the authors indicate we need more information on mechanisms of infection and virulence factors; data on variation among different hosts and pathogens; data on the effect of the environment on pathogen growth, survival and death; data from longer time frames to account for longer-term weather cycles; data on changing land use pattern advancement; improving sampling detection, quantification methods, and viability/infectivity assays; and continued developed of a thesaurus or lexicon of risk assessment

terms to facilitate the evolution of terminology. Appendix F1 also contains a very good list of general information on exposure analyses in Table F1.

Appendix G. Human Health Effects Annex.

This appendix contains a wealth of information on Human Health Effects as they impact the risk assessment process for microbial pathogens. There are excellent discussion on choosing a model for microbial dose-response; the non-threshold assumptions; sources of uncertainty in dose-response models; selection of dose-response data; animal studies; human studies; outbreak investigations; health surveillance data; and alternative dose-response models (empirical models; threshold models; mechanistic and physiologically-based models of infection; Bayesian models). This is one of the more comprehensive, detailed, and academic chapters in this document. It might be made a chapter in its own right. The writing style is very clear here and the material is very comprehensive and informative.