REVISED FRAMEWORK FOR MICROBIAL RISK ASSESSMENT

AN ILSI RISK SCIENCE INSTITUTE WORKSHOP REPORT

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An ILSI Risk Science Institute Workshop Report

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ABOUT ILSI AND THE ILSI RISK SCIENCE INSTITUTE

The **International Life Sciences Institute** is a nonprofit, worldwide foundation established in 1978 to advance the understanding of scientific issues relating to nutrition, food safety, toxicology, risk assessment, and the environment. By bringing together scientists from academia, government, industry, and the public sector, ILSI seeks a balanced approach to solving problems of common concern for the well-being of the general public.

Headquartered in Washington, D.C., ILSI is affiliated with the World Health Organization as a nongovernmental organization and has specialized consultative status with the Food and Agriculture Organization of the United Nations.

ILSI accomplishes its work through its branches and institutes. ILSI's branches currently include Argentina, Australasia, Brazil, Europe, India, Japan, Korea, Mexico, North Africa and Gulf Region, North America, North Andean, South Africa, South Andean, Southeast Asia, and Thailand, and a focal point in China. The ILSI Health and Environmental Sciences Institute focuses on global environmental issues.

The ILSI Research Foundation includes:

ILSI Allergy and Immunology Institute
ILSI Human Nutrition Institute
ILSI Risk Science Institute

The ILSI Center for Health Promotion comprises the Physical Activity and Nutrition Program and the Micronutrient Deficiency Program/Project IDEA (Iron Deficiency Elimination Action).

The ILSI Risk Science Institute (ILSI RSI) was established in 1985 to advance and improve the scientific basis of risk assessment. ILSI RSI serves as a catalyst for consensus on complex scientific issues in risk assessment by facilitating discussion and cooperation among scientists from all sectors.

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The steering committee for this activity included Mr. Gunther F. Craun (G. F. Craun & Associates), Dr. Alfred Dufour (EPA Office of Research and Development), Dr. Charles Gerba (University of Arizona), Dr. Charles Haas (Drexel University), Mr. Alan Roberson (American Water Works Association), Dr. Stephen Schaub (EPA Office of Water), and Dr. Mark Sobsey (University of North Carolina).

Drs. Susan A. Ferenc and David A. Neumann of ILSI RSI were responsible for convening and managing the activities of the steering committee, organizing the workshop, and assembling and editing this report. Dr. Stephen Schaub was the EPA project officer for this initiative, and Mr. Thomas Brosnan (ILSI RSI) assisted in facilitating the workshop. The case study of *Cryptosporidium* in drinking water was conducted by Drs. Peter F. M. Teunis and Arie H. Havelaar of the National Institute of Public Health and the Environment (RIVM), Bilthoven, The Netherlands. Mr. Jeffrey A. Soller, Dr. Joseph N. Eisenberg, and Dr. Adam W. Olivieri of EOA, Inc., Oakland, California, conducted the case study of rotavirus in drinking water. Dr. Jennifer Kuzma, National Academy of Sciences, provided technical assistance in the revision of the framework presented herein. Drs. Kelly Rhodes, Michelle Colby, and Roberta Morales of the University of Maryland developed the Glossary of Terms for Microbial Risk Assessment and the table of Synonymous Terms in Risk Assessment. Administrative and logistical support for this project was provided by Mss. Jennifer Allen, Eugenia Macarthy, Stephanie Carter, and Diane Dalisera of the ILSI RSI staff.

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1. INTRODUCTION

During 1995, the ILSI Risk Science Institute (ILSI RSI) and the U.S. Environmental Protection Agency (EPA) Office of Water developed a conceptual framework for assessing the risks of human disease following exposure to waterborne pathogens. The purpose of that initiative was to describe a generic approach to identifying scientific information that should be considered in attempts to quantitatively assess the human health risks associated with exposure to infectious agents in water. The resulting framework, the product of extensive deliberations by a 30-member working group of scientists from academia, industry, and government, was intended to be applicable to all types of microbial pathogens (i.e., viruses, bacteria, and eukaryotic organisms) and to all types of aqueous media (e.g., drinking water, recreational water, and sludge). The framework report, *A Conceptual Framework for Assessing the Risks of Human Disease Following Exposure to Waterborne Pathogens,* was submitted to the EPA Office of Water. A condensed version was subsequently published in *Risk Analysis* in 1996 [1].

To test the utility and flexibility of the framework, two quantitative risk assessments were commissioned in 1998. ILSI RSI contracted with two groups of investigators to conduct risk assessments in accordance with the guidance provided by the framework. Both groups were provided with plausible waterborne pathogen exposure scenarios. One group used various statistical methods to yield individual probabilistic estimates of human health risks associated with exposure to *Cryptosporidium* in drinking water [2]. The second group used an epidemiology-based state transition model to produce population-based estimates of human health risks associated with exposure to rotavirus in drinking water [3]. The investigators were asked to conduct the risk assessments in the context of evaluating the framework, i.e., by identifying the strengths and limitations of the framework and any unique insights that might be gained through its application. In both cases, final estimates of risk were secondary to the evaluation of the framework.

Both evaluations were presented at a two-day workshop held in Washington, D.C., on May 11–12, 1999. The purpose of the workshop was to review the utility and flexibility of the framework relative to the two commissioned evaluations, and to consider the applicability of the framework for microbial risk assessments performed for alternative routes of exposure. Participants in the workshop separated into three breakout groups: one examined the adequacy of the framework relative to the two case studies; the second explored the utility of the framework relative to microbiological hazards associated with exposure to other aqueous media, e.g., recreational water and sludge; and the third addressed whether and how the framework might be applied to foodborne microbes.

For each application, the groups considered (1) the utility of the framework, (2) any advantages or limitations that it might confer on resulting risk assessments, (3) whether any elements of the framework were essential or superfluous, (4) whether the utility of the framework could be enhanced through revision and what revisions might be recommended, (5) whether the framework provided a useful vehicle for conveying information between risk assessors and risk managers, and (6) whether, based on the likely application of the framework for conducting microbial risk assessments, critical research could be undertaken to enhance either the framework or the resulting risk assessment.

After a full day of deliberations, the chair of each breakout group reported on the group's conclusions and recommendations. Their findings are summarized in Section 2 of this report, Summary: Water- and Foodborne Pathogen Risk Assessment Workshop. All workshop participants agreed that (1) the utility and applicability of the framework could be enhanced with minor revisions to certain sections, (2) a glossary of terms relevant to microbial risk assessment should be created, and (3) a table of synonymous terms used in human health, animal health, and ecological risk assessment should be created as a resource for risk assessors from different disciplines.

Accordingly, the framework was revised to reflect the consensus-based recommendations emerging from the May 1999 workshop. The revisions consist of the introduction of new text, the modification of existing tables and figures, and the addition of several new tables. The intent was to enhance, through minor refinements and elaborations, the original framework that was submitted to the EPA Office of Water, recognizing that the framework

was the acknowledged work of a group of experts convened during 1995–1996. The Revised Framework for Microbial Risk Assessment and the newly created Glossary of Terms for Microbial Risk Assessment and the Table of Synonymous Terms in Risk Assessment were subsequently distributed for comment to workshop participants.

That review revealed that although the concepts embodied in the framework are sound, new data and new insights gained in the area of microbial risk assessment since 1995 suggest that the framework might further benefit from a more substantial revision. For example, the document could include more specific information on the various types of mathematical models that have been used in microbial risk assessments, address time-dependent aspects of infectious disease and immunity, and consider how animal reservoirs of disease and other factors might be incorporated into a risk assessment. A comprehensive review of the current literature and subsequent revision of the framework could form the basis for a future working group or expert panel. Such issues are clearly important and relevant, yet are beyond the scope of the current framework evaluation project. Hence, the revisions incorporated in the revised framework (Section 3 of this report) are limited to the consensus-based revisions identified during the May 1999 workshop.

The Revised Framework for Microbial Risk Assessment provides a useful and proven framework for conducting microbial risk assessments for various types of microorganisms under a variety of exposure scenarios. The revised framework, the companion glossary (Section 4), and the table of synonymous terms (Section 5) will likely prove to be important elements in the continuing development and evolution of microbial risk assessment.

References

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2. SUMMARY: WATER- AND FOODBORNE PATHOGEN RISK ASSESSMENT WORKSHOP MAY 11–12, 1999

Purpose and Format

The purpose of the Water- and Foodborne Pathogen Risk Assessment Workshop held on May 11–12, 1999, was to evaluate the usefulness of a conceptual framework for assessing the human health risks associated with exposure to water- and foodborne pathogens. This framework is described in the document *A Conceptual Framework for Assessing the Risks of Human Disease Following Exposure to Waterborne Pathogens.*

Quantitative risk assessments for *Cryptosporidium* and rotavirus in drinking water were conducted prior to the workshop to determine whether the framework is sufficiently robust to guide the risk assessment process for various types of microbial pathogens and exposure scenarios. On the first day of the workshop, these two risk assessments were presented, and the utility of the framework in helping structure and complete the assessments was evaluated. Risk assessments for *Salmonella enteritidis* in shell eggs, *Escherichia coli,* and *Listeria* were also presented.

During the remainder of the two-day workshop, three breakout groups met: the first to examine the strengths and limitations of the framework in the context of the two waterborne pathogen risk assessments, the second to determine the applicability of the framework for waterborne pathogen exposure scenarios other than drinking water, and the third to evaluate the usefulness of the framework for foodborne pathogen risk assessment. Workshop participants and observers are identified at the end of this section. Each group was charged with answering the following questions:

- Does the framework provide adequate guidance for conducting risk assessments for waterborne pathogens in drinking water or in other water exposure scenarios, or for foodborne pathogens?
- Would use of the framework likely provide advantages or impose limitations on the risk assessment process?
- Are there elements of the framework that are essential or superfluous in terms of conducting the risk assessments?
- Could the utility of the framework be enhanced by revising the framework? If so, what changes are recommended?
- Does the framework provide a useful means for communicating information about the risk assessment to risk managers?
- Are there critical research needs that, if addressed, would enhance either the framework itself or the resulting risk assessments?

The group chairs reported the conclusions and recommendations of the breakout group sessions in a final plenary session. Some general areas for improving the framework were agreed upon by all three groups. These consensus recommendations were incorporated into the original framework document and are discussed below. Other recommendations are also summarized below.

Consensus Conclusions and Recommendations

The groups agreed that the framework is useful for structuring risk assessments for waterborne pathogens and is sufficiently flexible for application to diverse exposure scenarios, including foodborne pathogens. However, revisions were suggested to improve the framework and increase its utility. General categories for these revisions were described by the breakout group chairs in the plenary session and in submitted written documents. The categories are summarized below.

Transparency

The breakout groups stressed the importance of transparency in the risk assessment process and recommended that the framework be revised to reflect this. For risk assessment to be transparent, methods and assumptions should be clearly stated and understandable to the intended audience, whether this consists of informed analysts in the field, risk managers, or the general public. The audience should be able to evaluate the adequacy of the data and methods from the provided information. The

framework was revised to include a discussion of the need for transparency.

Iterative Nature of the Risk Assessment Process

The groups pointed out that during any of the three phases of the risk assessment process—problem formulation, analysis, and risk characterization—other phases might be revisited and refined. For example, if during analysis new data are identified, the problem formulation might be revisited to design an input for these new data in the conceptual model. Likewise, during risk characterization, the final risk estimate might seem implausible. In this case, the analysis phase might be reviewed for errors or to incorporate better information. Therefore, the risk assessment process is not linear, but fluid and dynamic. The framework was revised to illustrate the iterative nature of risk assessment.

Importance of Model Development During Problem Formulation

The breakout groups noted that the original framework document does not adequately describe the development of a conceptual model during problem formulation. They suggested adding text to describe the importance of the conceptual model for depicting the purpose, defining the scope and scale, determining the appropriate variables, and identifying data needed for the assessment. The groups also noted that the conceptual model could serve as a basis for a preliminary or exploratory assessment, which can be conducted and used to further refine the conceptual model. The framework was revised by adding text to emphasize the importance of conceptual model development.

Importance of Input from Risk Managers During Problem Formulation

The breakout groups discussed the importance of input from risk managers during the problem formulation phase. Management objectives should be identified and discussed. Communication between the assessors and managers during this phase is important to identify questions that the assessment should answer and appropriate control measures that should be considered. Potential critical points of control should be identified in the conceptual model. Risk managers should play a key role during this phase. The framework was revised based on these recommendations.

Uncertainty and Variability

The breakout groups recommended more discussion of uncertainty and variability in the framework given their importance in modeling biological systems. Data limitations and incomplete knowledge of the underlying biological mechanisms of growth and disease can lead to great uncertainty in microbial risk assessments. Variability is a prominent factor in these risk assessments owing to the range of the genetic composition of hosts and pathogens, to various environmental conditions, and to different health conditions of individuals. The framework was revised to better discuss factors that contribute to uncertainty and variability.

Consideration of Control Processes During the Analysis Phase

The breakout groups discussed the effects of control processes on pathogen occurrence. It was noted that there was little discussion of these effects in the original framework document, yet some of the most important mitigation strategies may involve improving existing control processes or adding new control measures. The groups suggested that control processes (e.g., water treatment) should be considered in the framework, and text was added to revise the framework accordingly.

Factors in Dose-Response Modeling

The groups recommended that the dose-response discussion needed improvement in several areas. The use of animal models, albeit not ideal, is sometimes necessary, and therefore in the framework, animal models should not be discounted as an information source for dose-response modeling. Variability in hosts and pathogens should be emphasized, and the difficulties posed by this variability during dose-response modeling should be described. Likewise, uncertainty can result from extrapolating laboratory, clinical, or epidemiologic data to a particular host-pathogen interaction, because available data may not be designed for that specific interaction. These and other contributors to uncertainty should be mentioned. The importance of determining dose-response curves for subpopulations such as the immunocompromised, young, or elderly should be stated. The dose-response discussion in the text was revised in light of these recommendations.

Essential Elements of Risk Characterization

The groups identified some elements of risk characterization that were missing from the original framework document. Namely, the results of risk estimation should be evaluated for their plausibility by comparing them with any available exposure and illness data obtained during outbreaks. If the results are not realistic, the risk assessment model may need to be revised or additional data may need to be incorporated into the analysis. Risk management options should also be analyzed during risk characterization, and the variables that make the largest contributions to the overall risk should be identified. Sensitivity and uncer-

tainty analyses should be components of risk characterization. These elements were incorporated in revising the original framework document. In addition, a more detailed description of integrating the outcomes of health and exposure characterization in risk characterization was added.

Tables and Figures

As the breakout groups suggested, tables on dose response and risk characterization were added to depict the essential elements of these phases of the risk assessment process. In addition, at the recommendation of the breakout groups, the existing figures and tables were adjusted to more accurately reflect the text.

Glossary

The groups suggested that a glossary was needed to clarify the risk assessment terms used in the text. This glossary was compiled and appears in Section 4. Definitions for many of the terms were incorporated into the text of the revised framework. To be more consistent with other risk assessment documents and guidance, "pathogen risk assessment" was replaced by "microbial risk assessment."

Comparison of Synonymous Terms from Other Risk Assessment Paradigms

In addition to the above conclusions and recommendations, the groups recommended that synonymous terms from various risk assessment paradigms should be compared to decrease confusion caused by the terminology. The table that constitutes Section 5 was developed as the most appropriate way to depict this comparison; it illustrates the similarities and differences in terminology among human health, animal health, ecological, and other microbial risk assessment frameworks.

Other Conclusions and Recommendations

The following topics were identified by the individual breakout groups, but were not general consensus conclusions and recommendations and should not be construed as such.

Risk Communication

The need for good communication of the risk assessment process and results to interested and affected parties was stressed. The difficulties of communicating uncertainty and the feedback loop of communication between risk assessors, risk managers, and the general public were mentioned. It was suggested that a section concerning these and other elements of risk communication should be considered in the framework.

Threshold Versus Nonthreshold Dose-Response Modeling

Consideration of both nonthreshold and threshold models for dose-response analysis was suggested. It was noted that most current models presume a nonthreshold for infection—i.e., one organism can lead to infection—and that it might be mentioned in the text of the framework document that threshold models are also being developed.

Discrete Versus Continuous Dose and Exposure

It was noted that most dose-response data are based on single doses, whereas populations may be repeatedly exposed to certain microbial pathogens over time. A discussion of continuous and multiple exposures and their effect on the risk estimate was suggested.

Occupational Exposure

One group posed the question of whether the framework should be applicable to or should provide guidance for risk assessment of occupational exposures. These exposures represent another type of risk assessment, one that is complicated by scientific and regulatory considerations. The group thought that the framework was generally applicable to these exposures because it is flexible and adaptable.

Comparative Risk

One group suggested that the issue of comparative risks among different pathogens and different exposures should be considered in the framework. Common metrics that provide a basis for such comparisons—e.g., to compare *Vibrio vulnificus* and *E. coli* O157:H7—should be explored.

Restructured Figures and Tables

One group suggested that the five tables in the original framework be combined into three larger tables to reflect the three major phases of the risk assessment framework. It was also suggested that a table for problem formulation and its elements should be added.

Additional Revisions to the Framework

Secondary Transmission

One group believed that a limitation of the current framework was the incomplete discussion of secondary transmission. They noted that for some pathogens, secondary (or person-to-person) transmission is very important and should be addressed. Where appropriate, a mention of secondary transmission was added to the original framework.

Use of Surrogates

The use of surrogate or indicator species was discussed by one of the breakout groups. The group recommended emphasizing the limitations and assumptions associated with using a single pathogen as a representative for a class of pathogens or a nonpathogenic indicator species for a pathogen or pathogenic group. In addition, the group noted that the use of surrogates might be more appropriate for quantifying or predicting treatment efficacy than for predicting or quantifying health effects such as actual dose-response relationships. The group recommended the addition of a discussion of these and other issues concerning the use of surrogate or indicator species. A brief discussion of this issue was added to the text of the original framework.

Stepwise Approach to Risk Assessment

One breakout group had an extensive discussion about developing a stepwise approach to risk assessment. Problem formulation could include a preliminary assessment of health and exposure before moving into a full quantitative assessment. In essence, this first step would serve as a qualitative risk assessment. This stepwise approach was recommended as a means of prioritizing resources, identified by many countries as a constraint to conducting extensive risk assessments. A stepwise approach can be used to define the scope of the overall assessment and to determine whether enough information is available to conduct a comprehensive risk assessment. A general statement was added to the problem formulation phase in the original framework to introduce this possibility.

Research Needs for Conducting Microbial Risk Assessments

The three breakout groups were asked to identify research needs to enhance the effectiveness of the risk assessment process and, more specifically, the framework for microbial risk assessment. The following suggestions were made:

- Research on the use of safety or uncertainty factors for microbial risk assessment should be conducted. The circumstances for using such factors and the criteria to determine the magnitude of the factors should be considered.
- Model validation methods to compare the results of the risk assessment with "reality" should be explored. If few data exist for this comparison, after the risk assessment is conducted endpoints should be monitored so the model can be validated in the future.
- Qualitative assessment methods should be further developed, because quantitative data are not always available. Also, the use of risk assessment as a predictive tool or a prevention strategy should be considered.
- Criteria should be developed for the use of animal models for obtaining dose-response data. Better methods to extrapolate animal dose-response information to human dose-response models should be pursued, as well as better ways to address the uncertainty involved in such extrapolations.
- The issue of whether threshold or nonthreshold dose-response models are most appropriate should be explored for various pathogen-host combinations. In addition, alternative models for dose-response analysis and the effect of multiple exposure on the dose-response relationship should be investigated.

Other research needs identified by the breakout groups included information on mechanisms of infection, variation among different hosts and pathogens, and the effect of environment on pathogen growth, survival, and death.

Revised Framework

The workshop proved to be very useful for refining the original framework. The above conclusions and recommendations were used to revise the framework to more accurately reflect current thinking in microbial risk assessment. A glossary was added, and a comparison of synonymous terms in various risk assessment paradigms was added in the form of a table.

PARTICIPANTS IN THE WATER- AND FOODBORNE PATHOGEN RISK ASSESSMENT WORKSHOP, MAY 11–12, 1999, WASHINGTON, D.C.

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3. REVISED FRAMEWORK FOR MICROBIAL RISK ASSESSMENT

The Revised Framework for Microbial Risk Assessment adapted from *A Conceptual Framework for Assessing the Risks of Human Disease Following Exposure to Waterborne Pathogens* is presented in this section. The conclusions and recommendations from the Workshop on Water- and Foodborne Pathogen Risk Assessment (May 1999) were used to revise the original framework to more accurately reflect current thinking in microbial risk assessment.

Introduction

The potential for human disease associated with exposure to waterborne pathogenic microorganisms is a growing public health concern. This concern has been prompted in part by several recent outbreaks of cryptosporidiosis in the United States, the recent cholera epidemic in South America, and the general increased awareness of the breadth and magnitude of disease associated with waterborne pathogens [1–4]. In addition, as environmental control measures change in response to concerns about potential human health effects associated with chemical disinfection, concern is rising about the potential for exposure to pathogenic microorganisms. This heightened awareness has highlighted the need for the development of methods to assess the risk of human disease from waterborne pathogens, the efficacy of environmental control measures in reducing risk, and the relative risks of human disease associated with exposure to various disinfection by-products versus exposure to residual infectious microorganisms.

The process of quantitative risk assessment has been a valuable tool for assessing the human health effects associated with exposure to chemicals [5]. The information has been invaluable to decision makers responsible for developing regulatory standards, assessing treatment requirements, and conducting risk-benefit analyses. However, the development of an approach for assessing the human health effects associated with exposure to pathogens has received far less attention. A number of microbial risk assessments [6–9] have been conducted utilizing the conceptual framework that was developed for chemical risk assessments [5], which consists of four steps: hazard identification, dose-response assessment, exposure assessment, and risk characterization.

As these risk assessments have been developed, many complexities unique to the assessment of risks associated with exposure to microorganisms have been noted [7–10]. For example, one critical consideration is that because microorganisms are living organisms, their concentration can change through growth or death. A second consideration is that the distribution of pathogenic microorganisms in a water or food sample may be heterogeneous because of clumping or aggregation. In contrast, it is generally reasonable to assume that chemical agents are distributed uniformly within a water sample. A third consideration is that secondary transmission, or person-to-person transmission, may be important for pathogenic microorganisms, but not for chemicals. In addition, there is the potential for short- or long-term immunity from some infectious microorganisms. Given these differences and complexities, the question has arisen as to whether the conceptual framework outlined for chemical risk assessment is the most appropriate framework for the assessment of risks of human disease following exposure to pathogens.

To address this concern, the ILSI Risk Science Institute in cooperation with the U.S. Environmental Protection Agency (EPA) Office of Water convened a working group to develop a conceptual framework for assessing risks of human disease associated with waterborne pathogenic microorganisms. The working group was not asked to critically evaluate or develop specific analytical methods, but rather to take the opportunity to broadly consider the entire process of risk assessment as applied to waterborne pathogens. The working group was asked to consider a number of issues, including (1) the dynamic and iterative nature of the risk assessment process, (2) the role of risk managers, risk assessors, and stakeholders, (3) the interaction between the pathogen(s) of concern and humans, (4) the wide variety of potential scenarios such as the risk of human disease associated with pathogens in drinking water, recreational water, or sludge, (5) the questions that may need to be addressed in a risk assessment, and (6) the general information needed to address the questions. Discussions of these issues led to the devel-

opment of a conceptual framework, which is described below.

Conceptual Framework

Microbial risk assessment is a process that evaluates the likelihood that adverse human health effects will occur following exposure to a pathogenic microorganism or to the medium in which the microorganism occurs. Risk can be presented in several ways. Some risk assessments may provide probabilistic estimates of the likelihood of adverse effects; other risk assessments may provide a qualitative integration of exposure and effects. In all cases, the assessment should be transparent and understandable. Methods and assumptions should be clearly stated so that they can be understood by the intended audience and so that their appropriateness can be evaluated.

A conceptual framework for assessing the risks of human disease following exposure to water- and foodborne pathogens is shown in **Figure 1.** The framework is conceptually similar to the National Research Council (NRC) paradigm for human health risk assessments [5] as well as to the framework for ecological risk assessment developed by the U.S. EPA [11]. The risk assessment process involves three phases: problem formulation, analysis, and risk characterization. The analysis phase consists of two major elements: characterization of exposure and characterization of human health effects. Both of these elements are considered during problem formulation and risk characterization, where the exposure and human health effects elements are integrated to estimate risk (Figure 1). The microbial risk assessment process is iterative, as indicated by the double arrows in Figure 1. For example, if new information is obtained during analysis, the conceptual model developed during problem formulation may need to be reconsidered and revised to incorporate this new information. Likewise, if the results of the risk characterization seem implausible in light of available epidemiologic data and/or expert knowledge of the system, the analysis phase may be revisited and new data or methods used. The assessment is a learning process: iterative model refinement can provide insight into biological processes and causal relationships. Among the important results of a risk assessment are enhanced knowledge of the system and identification of areas where more research is needed. Three phases of microbial risk assessment are described below.

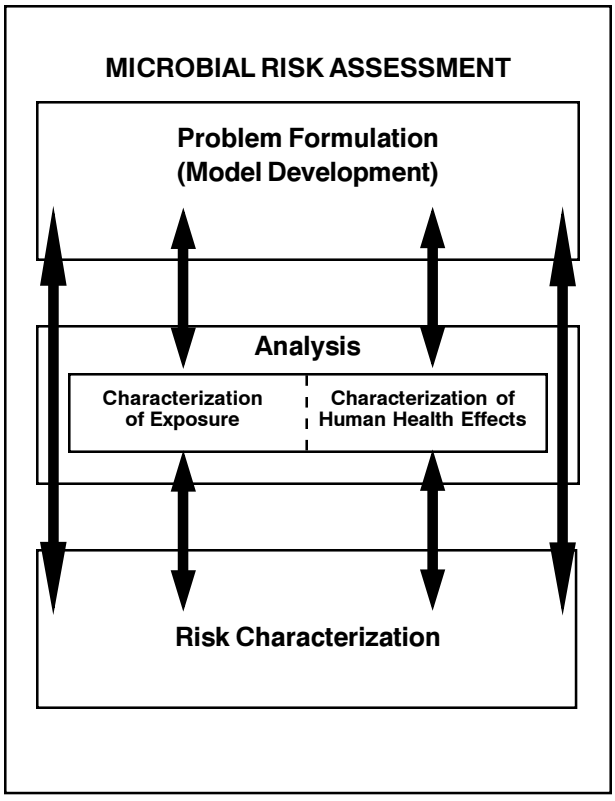

Figure 1. Generalized framework for assessing the risks of human disease following exposure to water- and foodborne pathogens

Problem Formulation

Problem formulation is the first phase of the microbial risk assessment. Problem formulation is extremely important; it is a systematic planning step that identifies the goals, breadth, and focus of the risk assessment, the regulatory and policy context of the assessment, and the major factors that will need to be addressed for the particular assessment. Risk assessments can be qualitative or quantitative, depending on the data and methods used, and are initiated for a variety of reasons. For example, it may be necessary to assess the potential for human risk associated with exposure to a known pathogen. Alternatively, a risk assessment may be initiated because of an outbreak where the specific pathogen or vehicle of infection (medium of concern) may be unknown. The risk assessment process may also be initiated to determine critical points for control, such as watershed protection measures and specific water or food treatment processes to reduce, remove, or inactivate various pathogens. Many other reasons exist, and the specific risk assessment to be developed for each of these situations would be quite different because of the available database, the questions that need to be addressed, and the information required to address the questions. Therefore, a critical component of the problem formulation phase is to determine the purpose of the risk assessment and the unique questions that the risk assessment needs to address.

Once the purpose of the risk assessment is defined, the motivating factors for conducting the risk assessment are taken into consideration during development of a conceptual model. The conceptual model describes the inter-

actions of a particular pathogen or medium and a defined population within a defined exposure scenario. An initial characterization of exposure and health effects is conducted. Pathogen characteristics (such as taxonomy, ecology, and survival and growth characteristics), host characteristics (such as nutritional and immune status), and host-pathogen interactions (such as virulence, host specificity, and infection mechanism) are considered. The exposure scenario(s) and health effects are defined, including the media, exposure routes, endpoints, and key assessment variables. The conceptual model is used to address the data needs for the assessment. The estimated quality and quantity of data to be analyzed and the potential sources and types of variability and uncertainty should be stated.

To guide model development, the scope and scale of the assessment are determined. For example, the scale, or magnitude, of the assessment may involve certain target populations or geographic regions. The scope, or breadth, of the assessment determines which exposure pathways and adverse consequences are of concern. The model also describes the specific questions to be addressed, the relevant information needed, the methods that will be used to analyze the data, and the assumptions inherent in the analysis. It defines the inputs, outputs, and endpoints of the assessment, and possible exposure pathways. Inputs are the data and information that go into the assessment, and outputs are the data and information obtained from the assessment. Endpoints are the final adverse effects that are quantified in risk estimation (e.g., human morbidity or mortality). Exposure pathways for pathogens may include both primary routes (e.g., water or food consumption) and secondary routes (e.g., person-to-person contact) of transmission. For some pathogens, secondary transmission is likely, and it will be important to include this route in the conceptual model. A preliminary or exploratory assessment, whether quantitative or qualitative, may be used during problem formulation to evaluate and, if needed, to refine the conceptual model. This preliminary assessment may serve to identify data gaps and prioritize resources for the assessment. Development of a complete and accurate conceptual model is important because it provides direction for the next phase of the assessment, analysis.

To be meaningful and effective, microbial risk assessments must be relevant to regulatory and public health concerns, as well as scientifically valid. Although risk assessment and risk management are distinct processes, establishing dialogue among risk assessors, risk managers, and other stakeholders during the problem formulation phase can ensure that both societal and scientific goals are met. The risk managers can ensure that the risk assessment considers and provides information necessary for making policy decisions, and the risk assessors can ensure that the appropriate scientific concerns are addressed. Any current processing controls for water or food should be identified and considered in the analysis. During discussions between risk assessors and risk managers, the conceptual model may be used to determine which mitigation or control measures should be considered during the assessment. These risk management options can be incorporated into the model and evaluated during the analysis and risk characterization phases. It is important that communication between risk assessors and risk managers take place during all phases of the assessment, not only during problem formulation.

In addition to risk managers, other stakeholders can provide insight into the scale of the problem and the resources necessary to generate data for the assessment. All perspectives are necessary to ensure the appropriate use of resources to produce scientifically sound risk assessments that are relevant to risk management decisions and public concerns.

Analysis Phase

The analysis phase of the microbial risk assessment consists of the technical evaluation of data concerning the potential exposure and associated health effects, and is based on the conceptual model developed during problem formulation. This phase consists of two elements: characterization of exposure and characterization of human health effects (**Figure 2**). However, analysis of the two elements must be an interactive process to ensure that the analyses are compatible, as illustrated by the dashed line in Figure 2.

Both the characterization of exposure and the characterization of human health effects are influenced by the analytical methods and/or tools that are available (Figure 2). This is an iterative process in that as information is analyzed with available methods, the information in turn provides fuel for the development of more refined methods; this then leads to the refinement of the analysis. For example, an exposure assessment may be modified as a result of improved methods for the enumeration of a particular pathogen, and a health assessment may be modified as a result of new information on infective dose levels. During the analysis phase, the limitations of the data and methods used should be discussed.

Characterization of Exposure

Characterization of exposure involves an evaluation of the interaction between the pathogen, the environment, and the human population. Three elements of analysis may be involved: pathogen characterization, pathogen occurrence, and exposure analysis (Figure 2). The specifics of the analysis will depend on the scenario(s) developed during problem formulation. Analysis of the elements

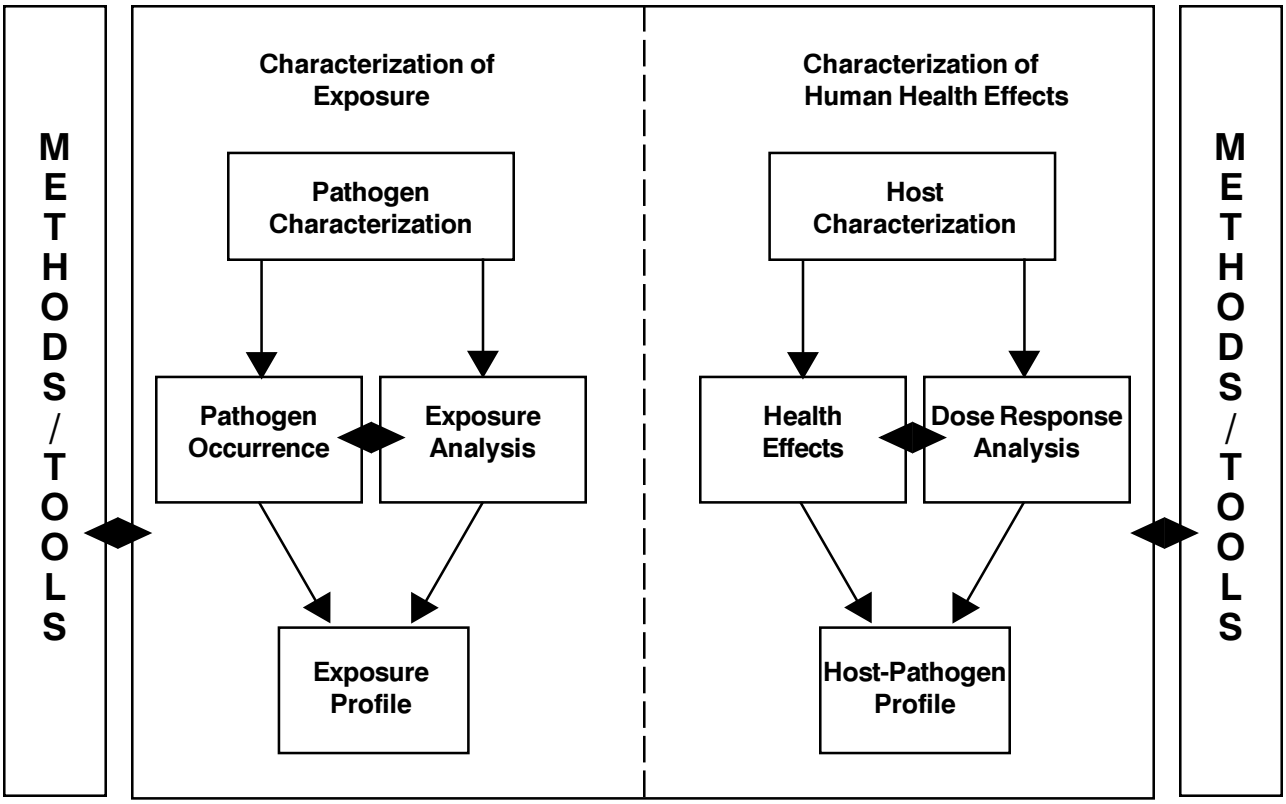

Figure 2. Analysis phase of microbial risk assessment for water- and foodborne pathogens

is an interactive process, as depicted by the arrows in Figure 2. Characterization of exposure culminates in the development of an exposure profile that quantitatively or qualitatively evaluates the magnitude, frequency, and pattern of human exposure for the scenario(s) developed during problem formulation and serves as input for risk characterization.

Pathogen Characterization. Pathogen characterization involves determination of the characteristics of the pathogen that affect its ability to be transmitted to and cause disease in the host. The ability of a pathogen to cause disease is influenced by many factors **(Table 1**). Some of these factors relate to the intrinsic properties of the pathogen, such as phenotypic and genetic characteristics that influence virulence and pathogenicity, and host specificity. Microbial growth, survival, and death are critical components of microbial risk assessment, and during pathogen characterization, these characteristics are evaluated under different environmental conditions, such as temperature and nutrient availability. The ability of the pathogen to survive and multiply in the environment based on its resistance to control processes is determined. These control processes, in turn, may alter virulence and pathogenicity. Host specificity, infection mechanisms, potential for secondary transmission, strain variation, and ecology are other characteristics that may be considered. The specific characteristics that are evaluated will depend on the scenario that is delineated during problem formulation and on the biology of the organism.

Pathogen Occurrence. Pathogen occurrence involves describing the occurrence of a pathogen in a medium, including identification of peaks, average levels, frequency distribution, seasonal variation, and association with other temporal or spatial changes (**Table 2**). As part of pathogen occurrence, it may be necessary to determine the concentration of the pathogen in the environmental media of interest and the potential source of the pathogen. Such estimates can be influenced by the physical state of the

Table 1. Elements That May Be Included in Pathogen Characterization

- Virulence and pathogenicity of microorganism
- Pathologic characteristics/diseases caused
- Survival and multiplication
- Resistance to control or treatment processes
- Host specificity
- Infection mechanisms/route of infection/portals of entry
- Potential for secondary spread
- Taxonomy/strain variation
- Ecology

Table 2. Elements That May Be Included in Pathogen Occurrence

- Temporal distribution/frequency
- Concentration in environmental media
- Spatial distribution
  - clumping, aggregation, particles, clustering
- Niche
  - ecology and non-human reservoirs
- Survival, persistence, and amplification
- Seasonality
- Meteorological and climatic events
- Presence of control or treatment processes
  - including their reliability and variability
- Indicators and/or surrogates for indirect evaluation

Table 3. Elements That May Be Included in Exposure Analysis

- Identification of media
- Units of exposure
- Route of exposure
- Size of exposed population
- Demographics of exposed population
- Spatial and temporal nature of exposure
  - whether single or multiple exposure
- Behavior of exposed population
- Treatment, processing, and recontamination

pathogen in the environment. For example, aggregation or particle association can provide protection from environmental control measures and can also result in a higher exposure than suggested by analytical results. A thorough understanding of the niche of a pathogenic microorganism may also be important for some assessments. For example, some assessments may be concerned with evaluating a particular construction material or product design that can greatly affect the ability of pathogens to survive and multiply. For example, crevices in equipment can protect pathogens from control treatments, or certain equipment materials can affect pathogen growth. Also relevant to a determination of pathogen occurrence is information on the ability of a pathogen to survive, persist, and multiply. Other variables affecting occurrence are seasonal, geographic, and climate related. When information on a particular pathogen species of interest is lacking, it may be necessary to use occurrence data for surrogate or indicator species. The limitations and uncertainty associated with those data and their use should be considered.

Control processes, such as water treatment, may have significant effects on pathogen occurrence and should be considered. Variability and reliability of control processes and the interdependence of multiple control processes may be analyzed, as well as the potential for recontamination after treatment.

The outcome of pathogen occurrence is an evaluation of all relevant factors pertaining to the occurrence and distribution of the pathogen.

Exposure Analysis. Exposure analysis involves characterizing the source and temporal nature of human exposure to pathogenic microorganisms. Many elements may be included in the analysis (**Table 3**). Where possible, the vehicle, such as drinking water or food, is identified as well as the associated unit and route of exposure (e.g., number of glasses of water consumed or number of food servings). In addition to drinking water, other exposure media include recreational and reclaimed water, sludge and nonwater media such as biosolids and manure. The size and demographics of the population at risk should be determined. Consideration of the temporal nature or duration of exposure, route of exposure, and transmission potential may also be important. For example, a single oral exposure to certain pathogens with high transmission potential may have substantially different consequences than multiple exposures to pathogens with low transmission potential. Of course, route of exposure and transmission potential will in turn be influenced by the behavioral characteristics of the potentially exposed human population.

Exposure Profile. The exposure profile provides a qualitative and/or quantitative evaluation of the magnitude, frequency, and patterns of exposure to a pathogen for the scenario(s) developed during problem formulation. The profile draws on information obtained from the pathogen characterization, pathogen occurrence, and exposure analysis phases. A critical component of the exposure profile is an assessment of the assumptions and uncertainties that are made during the analysis. In many assessments, relevant data may not be available for all aspects of the analysis and/or the data may be of questionable quality. Consequently, a number of assumptions may be made, each with varying degrees of associated uncertainty. These assumptions should be based on scientific judgment and described in the exposure profile for consideration in risk characterization. The uncertainty analysis identifies, and to the extent possible quantifies, the uncertainty associated with each element of the exposure assessment, as described by Finkel [12] and the National Research Council [13]. This may include quantification of uncertainties associated with errors introduced as a result of study design, errors associated with estimates of the concentration of the pathogenic microorganism, or errors associated with estimates of human ingestion volumes. The uncertainty analysis is described in the exposure profile and provides insight into the strengths and weaknesses of the assessment for consideration in risk characterization.

Characterization of Human Health Effects

Characterization of human health effects involves the interactive analysis of three critical components: host characterization, evaluation of human health effects, and quantification of the dose-response relationship (Figure 2). This phase culminates in the development of a host-pathogen profile that provides qualitative and/or quantitative descriptions of the nature of the illness and quantitative dose-response analyses for the scenario(s) developed during problem formulation, and serves as input for risk characterization.

Host Characterization. Host characterization involves an evaluation of the characteristics of the potentially exposed human population that may influence susceptibility to a particular pathogen. Susceptibility is the extent to which a host is vulnerable to infection by a pathogen, taking into account a host's intrinsic and/or acquired traits that modify the risk of infection or illness. It is important to recognize that host factors may be more important in determining the severity or outcome of an infection than in determining the likelihood of infection. High-risk groups may develop severe symptomatic illness, whereas low-risk groups may develop asymptomatic infections or mild illness. There are many factors that can influence susceptibility and severity (**Table 4**), although not all of them will be important for all pathogens. Age is an important consideration, since the risk of disease is often far greater for the young and the old. Susceptibility may be influenced by the status of the immune system, and therefore knowledge of immune status, concurrent or recent infections, and use of medications may be important. Other factors that may influence susceptibility and that should be considered in host characterization include genetic predisposition, pregnancy, and nutritional status. Finally, the analysis may consider whether and how demographics or social and/or behavioral traits influence susceptibility or severity.

The outcome of host characterization is the identification of factors that influence susceptibility and severity and the identification of susceptible subpopulations. Both of these are important for the assessment of health effects.

Health Effects. The clinical illness associated with a pathogen or medium is characterized in the health effects phase (**Table 5**). When possible, the characterization should consider the whole spectrum of clinical manifestations, including symptomatic and asymptomatic infections, duration and severity of clinical illness, mortality, and sequelae. In most cases, the assessment of health effects will rely on epidemiologic and clinical information. Several epidemiologic study designs may be employed in the assessment of human illness, and each is associated with certain strengths and limitations. For example, data for characterizing clinical illness may be available from a clinical or epidemiologic study, such as a controlled clinical study to determine infective dose or an intervention study to compare the effects of improved water treatment or quality. In these studies, it is possible to control for the health and immune status of individuals, as well as the dose, route of exposure, and time of exposure. However, difficulties may be encountered in the extrapolation of these data to a natural setting owing to uncertainties associated with small sample size, the degree to which the response of the population studied is predictive of the potential response of the population at risk, and the similarity between the laboratory strain of the pathogen and the strains in the environment. In other cases, data may be available only from outbreaks. These clinical and epidemiologic studies provide the opportunity to obtain data in a natural setting, and have many strengths, including the ability to assess susceptible subpopulations, seasonality of the pathogen, and secondary transmission. However, they are limited by difficulties in recognizing an outbreak and the full spectrum of an illness and by the lack of knowledge concerning exposure. Regardless of study type, the strengths and limitations of the studies should be considered in the assessment, including evaluations of the statistical power of the study and the appropriate control of systematic bias, especially confounding and misclassification.

Consideration of the severity of the illness associated with a particular pathogen may be important. Severity of illness is defined as the degree or extent of clinical disease produced by an infectious microorganism, and

Table 4. Elements That May Be Included in Host Characterization

- Age
- Immune status
- Concurrent illness/medical treatment
- Genetic background
- Pregnancy
- Nutritional status
- Demographics of exposed population
- Social/behavioral traits

Table 5. Elements That May Be Included in Health Effects

- Duration of illness
- Severity of illness
- Infectivity
- Morbidity, mortality, sequelae of illness
- Extent or amount of secondary transmission
- Quality of life

can be expressed in a variety of ways. Some pathogens may be associated with a high degree of mortality, and therefore severity may be expressed as mortality rate. Other pathogens may be associated with gastrointestinal distress, and severity may be expressed as the proportion of the population affected or duration of illnesses. In addition, the potential for long-term illness may exist, in which case severity may be expressed in terms of the cost to society, such as the proportion of workdays lost or the cost of treatment. When severity is highlighted as a consideration during problem formulation, it is important that the assessment include a definition of the severity scale used and how it is measured, as well as the associated assumptions and uncertainties.

For pathogens that cause long-term chronic illness, it may be desirable to include an assessment of the quality of human life during the illness. Quality of life may be expressed in a variety of ways, depending on the nature of the illness. For some pathogens, human life expectancy may decrease, chronic debilitation may occur, or quality of life may be affected by episodic bouts of disease. When included in an assessment, the definition of quality of life should be stated as well as the associated assumptions and uncertainties.

Dose-Response Analysis. This analysis characterizes the relationship between dose, infectivity, and the manifestation and magnitude of health effects in an exposed population. Elements of dose-response analysis are shown in **Table 6.** This relationship is complex, and in many cases a complete understanding will not be possible. Data obtained from animal studies, human clinical studies, and outbreaks are used to generate a curve or model for the quantitative relationship between dose (the amount of a pathogen that enters or interacts with a host) and a response (such as infection or illness).

Animal models may be useful for determining these relationships, but should be interpreted with caution because of the host specificity of most pathogens. Therefore, when clinical or epidemiologic data are available, dose-response analyses will generally be based on such data. These analyses will be affected by the quality and quantity of data available for the assessment of human health effects, and at least in some cases, knowledge of the actual dose may be limited. For example, human outbreak studies may provide only crude, indirect measures for dose-response assessment, such as number of glasses of water consumed. Similar restraints exist for population experimental, cohort, and case-control studies. For laboratory studies, the route of administration and preparation of inoculum may also affect the dose-response relationship. Expert opinion can be used as a source of information for dose-response modeling in the absence of sufficient data.

Table 6. Elements That May Be Included in Dose Response Analysis

- Statistical model(s) to analyze or quantify dose-response relationships
- Human dose response data
- Animal dose response data
- Utilization of outbreak or intervention data
- Route of exposure or administration
- Source and preparation of challenge mateial or inoculum
- Organism type and strain
  - including virulence factors or other measures of pathogenicity
- Characteristics of the exposed population
  - age, immune status, etc.
- Duration and multiplicity of exposure

In situations where the actual dose of a microorganism ingested is known, such as in human feeding studies, there may be uncertainties associated with the use of laboratory strains of the pathogen as well as with how predictive the response of a carefully selected test human population is of the population at risk. Even within the same species and subspecies, different strains of pathogenic microorganisms may have different characteristics that cause variation in their ability to enter and infect the host and cause disease (see the pathogen characterization elements listed in Table 1). Therefore, it is important to use strains that are identical or closely related to the strain of concern. Likewise, the human subjects in laboratory feeding studies will vary according to their genetic background, immune and nutritional status, and overall health (see the host characterization elements listed in Table 4). These differences will affect the results of laboratory feeding studies, especially when a small number of people are the subjects of such studies. Whenever possible, large numbers of heterogeneous subjects who represent the variability in the population of interest should be used.

Variability in hosts and pathogens may necessitate more than one dose-response curve in a given assessment. For example, distinct dose-response curves can be determined for special subpopulations such as children, pregnant women, or the immunocompromised. In addition to variability, extrapolating human or animal laboratory data to whole populations leads to uncertainty in the dose-response curve. The magnitude of the uncertainty will depend on the quantity and quality of the data. These uncertainties can be quantified by using statistical and/or Monte Carlo techniques to generate a range of possible dose-response curves.

Another difficulty that may be encountered in a dose-response analysis is the availability of data regarding in-

fection. In many cases, infection data will not be available, so the analysis may only be able to describe the relationship between dose and clinical illness, rather than dose, infection, and clinical illness. Other special considerations for microbial dose-response modeling include the effect of very low doses on different subpopulations, whether there is a threshold dose for a given response, and previous or multiple exposures to a pathogen that might lead to immunity in the host.

In light of the importance of making the risk assessment transparent, the dose-response analysis should clearly identify how the information was obtained and state what the assessment is based-on. In addition, the assumptions that are made, as well as the associated uncertainties, should be thoroughly described.

Host-Pathogen Profile. Using information obtained from the host characterization, the assessment of human health effects, and the dose-response analysis, the host-pathogen profile provides a qualitative and/or quantitative description of the nature and potential magnitude of adverse human health effects for the scenarios developed during problem formulation. Critical components of the host-pathogen profile are an assessment of the assumptions made during the analysis and the uncertainty associated with the analysis because of lack of knowledge of the system or insufficient experimental data. In many assessments, relevant data may not be available for all aspects of the analysis and/or the data may be of questionable quality. Consequently, a number of assumptions may be made based on scientific judgment, and these should be described in the host-pathogen profile. The associated uncertainties should be described and quantified where possible [12, 13]. The uncertainty analysis is included in the profile and serves as input for risk characterization.

Risk Characterization

Risk characterization is the final phase of the microbial risk assessment and results from combining the information from the exposure profile and the host-pathogen profile (**Table 7**). Risk characterization consists of two major steps: risk estimation and risk description. Risk estimation describes the types and magnitude of effects anticipated from exposure to the microbe or medium and can be qualitative or quantitative depending on the data and methods used. During this phase, the likelihood of adverse human health effects occurring as a result of a defined exposure scenario to a microbial contaminant or medium is evaluated. To do this evaluation, the results from the analysis phase for exposure characterization and health characterization are combined. For example, the results from characterization of exposure can be expressed as the number of organisms to which an individual is exposed in a defined amount of time and given certain consumption rates.

Table 7. Elements That May Be Included in Risk Characterization

- Evaluate health consequences of exposure scenario
  - risk description (event)
  - risk estimation (magnitude, probability)
- Characterize uncertainty/variability/confidence in estimates
- Conduct sensitivity analysis
  - evaluate most important variables and information needs
- Address items in problem formulation
- Evaluate various control measures and their effect on risk magnitude and profile
- Conduct decision analysis
  - evaluate alternative risk management strategies

The results from characterization of human health effects can be expressed as the probability of individual illness after a certain number of organisms are consumed. During risk estimation, these two results can be mathematically combined to obtain the probability of human illness for a defined exposure scenario. The final result can be expressed as an individual risk estimate (e.g., one in a million probability of illness) or as a population risk estimate (e.g., 10 illnesses per year in a certain region). Alternatively, risk from pathogenic microorganisms can be modeled dynamically to consider the individual within a community rather than as an isolated individual. Time-dependent elements such as secondary transmission, host immunity, and animal reservoirs are included in dynamic models. All assumptions that were made throughout the risk assessment are clearly identified, and their impact on the assessment is described. The second component of risk characterization, risk description, involves describing the event according to its nature, severity, and consequences.

Uncertainties associated with problem formulation, analysis, and risk characterization are identified and quantified where possible. Variability, defined as observed differences attributable to true heterogeneity or diversity in a population or exposure parameter, is also quantified where possible. Confidence in the risk estimates is expressed in the risk description through a discussion of the weight of the evidence. This includes consideration of the sufficiency and quality of the data, and evidence of causality. The limitations of the analysis based on the quality and quantity of data should be acknowledged. The final risk estimates should be evaluated for plausibility and how closely they compare to any available exposure and illness data obtained during outbreaks. If the results are not comparable, it may be necessary to revise the model developed during problem formulation or to reconsider the data and methods used during analysis.

Variables used for data input can be evaluated for their effects on the final risk estimates. Sensitivity analyses can be used to determine the quantitative contribution of variables to the overall risk, and to indicate where more data are needed. The assessment process is by nature iterative, and it may be useful to return to the analysis phase and collect and incorporate more data or information for the most sensitive variables. This new information can serve to reduce the uncertainty associated with the assessment. Variability cannot be reduced, but more information can be used to better characterize it.

Finally, the risk characterization should include a discussion of whether the assessment adequately addresses the questions delineated during problem formulation. In particular, the risk management options defined during problem formulation should be used to compare risk estimates with and without the various existing and proposed control measures. These decision analyses can be used to address the management objectives that were the reasons for conducting the assessment. The most sensitive variables, or the variables with the largest contribution to the overall uncertainty in the risk estimate, may provide risk managers with guidance for investing resources for research or for developing better control processes. As new data become available or as risk managers ask new questions, given the iterative nature of the process, the problem formulation and analysis phases can be revisited and the assessment revised.

Future Directions

The working group successfully developed a conceptual framework for assessing the risks of human disease following exposure to waterborne pathogenic microorganisms. The framework is conceptually similar to the framework developed for chemical risk assessment [5] and the framework for ecological risk assessment [11], in that each includes exposure and effects assessments. Each framework is tailored to address concerns specific to chemicals, ecological systems, or pathogens. However, the framework developed in this document can be adapted and applied to microbial risk assessments for various occupational and recreational water exposures, as well as for exposures to pathogens in other media such as food. The inclusion of a problem formulation phase is similar to the framework for ecological risk assessment, and this recognizes the need for a dialogue among the risk manager, the risk assessor, and the stakeholders to utilize resources to produce scientifically sound risk assessments relevant to management decisions and public concerns. The framework emphasizes the dynamic and iterative nature of the risk assessment process, and allows wide latitude for planning and conducting risk assessments in diverse situations, each based on the common principles discussed in the framework.

Future efforts need to be directed toward the examination of methods for estimating risk and ways to improve the estimates. Recent risk assessments of pathogens in drinking water have been based on a series of probability functions [6–9]. One important step during the analysis phase of such investigations is to define the probability of infection following ingestion of a given dose of a pathogen; this is described by application of the beta-Poisson model, although other models are available. Another important step is to ascertain the relationship between infection and progression to clinical disease. This relationship is described as a conditional probability that once infected, a particular individual contracts a disease. A common assumption inherent in this approach is that the chance of contracting a disease (once an individual is infected) is independent of the ingested dose, although the scientific evidence for this assumption is equivocal. Further understanding of the relationship between infection and subsequent illness is needed to evaluate the impact of this assumption.

Dynamic models that relax this assumption of independence and incorporate medical status and immune responses may be used as alternatives to this approach. There is a need to develop methods to incorporate the impact of critical susceptibility factors such as age and immune status, which are currently not accounted for. Many current microbial risk estimates are based on the assumption that the probability of infection or illness resulting from exposure is independent of previous exposures, and that probability of infection or illness resulting from secondary transmission is also independent of previous exposures. These assumptions ignore the possibility of temporary or permanent immunity, and dynamic methods for incorporating such information may greatly improve risk estimates. In addition, methods and models for incorporating information on secondary transmission are needed. Finally, there is a need to develop methods to account for the heterogeneous distributions of microorganisms and the potential changes in concentration of microorganisms in the environment.

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4. GLOSSARY OF TERMS FOR MICROBIAL RISK ASSESSMENT (MRA)

This glossary is intended to be a companion document to the Revised Framework for Microbial Risk Assessment. Many of the terms listed in the glossary are used in the framework whereas others are part of the language used in microbial risk assessments. All are defined to facilitate mutual understanding of terms used by microbiologists as well as risk assessors. Definitions attributed to other authorities are referenced; terms defined in the context of the framework are given without attribution.

Amplification Multiplication or replication of a microorganism within a given medium.

Analysis phase (of microbial risk assessment) A component of microbial risk assessment consisting of the technical evaluation of data concerning potential exposure and associated health effects. Elements of this process are characterization of exposure and characterization of human health effects.

Attack rate The proportion of an exposed population at risk who become infected or develop clinical illness during a defined period of time.

Characterization of exposure A component of the analysis phase of microbial risk assessment that evaluates any interactions between the pathogen, the environment, and the human population. Steps in this process are pathogen characterization, determination of pathogen occurrence, and exposure analysis; the result is an exposure profile.

Characterization of human health effects A component of the analysis phase of microbial risk assessment that evaluates the ability of a pathogenic microorganism to cause adverse human health effects under a particular set of conditions. Steps in this process are host characterization, evaluation of human health effects, and quantification of the dose-response relationship; the result is a host-pathogen profile.

Clinical illness Deviation from the normal healthy state, manifested as symptomatic disease.

Cross contamination Direct or indirect transfer of a pathogen from one medium (e.g. food or water) to another.

Disease Any deviation from or interruption of the normal structure or function of any part, organ, or system (or combination thereof) of the body that is manifested by a characteristic set of symptoms and signs and whose etiology, pathology, and prognosis may be known or unknown. [1]

Distribution (spatial or temporal) The arrangement in space and time of a specific microorganism or disease caused by that microorganism.

Dose The amount of a pathogen that enters or interacts with an organism.

Dose-response A relationship in which a change in amount, intensity, or duration of exposure to a pathogen is associated with a change in the manifestation and magnitude of human health effects.

Dose-response analysis The process of characterizing the relation between pathogen dose, infectivity, and the manifestation and magnitude of health effects in an exposed population, including estimating the incidence of the health effects as a function of exposure to the pathogen.

Exposure analysis The process of characterizing the source and temporal nature of human exposure to a pathogenic microorganism.

Exposure profile A qualitative and/or quantitative evaluation of the magnitude, frequency, and pattern of exposure to a pathogen, developed during the analysis phase of microbial risk assessment, including a description of the assumptions and uncertainties inherent in such an evaluation.

Food ecology The study of the interactions between factors inherent (pH, water activity, nutrients) in or external (temperature, gaseous environment) to a food and the composition of its specific microbial population.

Foodborne pathogen A microorganism that is capable of causing disease and that is transmissible by ingestion of food.

Health effect The clinical manifestation of disease associated with a specific pathogen, including symptomatic and asymptomatic infections, clinical illness, mortality, and sequelae.

Host A person or other living animal, including birds and arthropods, that affords subsistence or lodgment to an infectious agent under natural conditions. In an epidemiologic context, the host may be a population or a group. [2]

Host characterization Evaluation of the characteristics of a potentially exposed human population that may influence susceptibility to a particular pathogen.

Host pathogen profile A qualitative and/or quantitative evaluation of the nature and potential magnitude of human health effects associated with specific pathogen exposure.

Host specificity The characteristic of a pathogen that renders it capable of infecting one or more specific hosts.

Immunity (protective) State of specific resistance to infection and infectious disease resulting from prior exposure to a pathogen and/or pathogen-derived toxins.

Immunocompromised A state of reduced immune responsiveness as a result of inherited defects, infection, administration of immunosuppressive drugs, irradiation, malnutrition, or certain disease processes.

Infection (mechanism of) The process by which a microorganism establishes itself in a host, including transmission, invasion, and multiplication.

Infectivity The characteristic of a microorganism that allows it to infect and subsequently survive and multiply within a susceptible host. [3]

Methods A systematic procedure or mode of inquiry used in microbial risk assessment.

Microbial risk assessment A process that evaluates the likelihood of human health effects occurring after exposure to a pathogenic microorganism or to a medium in which pathogens exist.

Pathogen (frank) A microorganism capable of producing disease in both healthy and compromised persons.

Pathogen (opportunistic) A microorganism that does not ordinarily cause disease but that, under certain circumstances (e.g., impaired immune response resulting from other disease or drug treatment), elicits a pathogenic response.

Pathogen characterization Evaluation of the characteristics of a pathogen that affect its ability to be transmitted to and cause disease in the host.

Pathogen occurrence A description of the frequency of appearance of a pathogen in a medium, including identification of peaks, average levels, frequency of detection, distribution, seasonal variation, and association with other temporal or spatial changes.

Pathogenicity The property of an infectious agent that determines the extent to which overt disease is produced in an infected population or the power of the organism to produce disease. [4]

Persistence The ability of a pathogen to remain in a host or in the environment for extended periods of time.

Predictive microbiology Analytical methods including mathematical modeling to estimate changes in bacterial numbers under different environmental or processing conditions, thus allowing assessment of the degree of contamination of a given medium.

Primary transmission Direct or indirect transfer of a food- or waterborne pathogen from a contaminated medium to a susceptible host, whether or not disease is produced.

Probability of illness The likelihood that a susceptible host will develop symptomatic disease given sufficient exposure to a particular microorganism.

Probability of infection The likelihood that a particular microorganism will successfully establish itself in a given host or population.

Problem formulation (of microbial risk assessment) A systematic planning step that identifies the goals, breadth, and focus of the microbial risk assessment, the regulatory and policy context of the assessment, and the major factors that will need to be addressed for the assessment.

Reservoirs Any biological or environmental milieu that supports the maintenance and/or growth of pathogenic organisms. Such reservoirs can be the sources of both epidemic and endemic infections.

Resistance (to infection) The sum total of body mechanisms that interpose barriers to the invasion or multiplication of infectious agents or to damage by their toxic products. [4]

Resistance (of pathogens) The ability of a microorganism to adapt to and overcome the effects of antimicrobial drugs and/or host immune responses.

Risk The product of the likelihood of the occurrence and the magnitude of the consequences of exposure to a pathogen on human health.

Risk characterization (of microbial risk assessment) Estimation of the likelihood of adverse human health effects occurring as a result of a defined exposure to a microbial contaminant or medium.

Route of exposure The pathway (e.g., ingestion, inhalation, dermal) or vehicle by which a pathogen comes into contact with a host organism (e.g., food, soil, fomites, water).

Secondary transmission Direct or indirect propagation of a pathogen from an infected person (with or without clinical illness) to additional people.

Severity of illness The degree or extent of clinical disease produced by an infectious microorganism or toxin. Severity of illness does not necessarily reflect severity of infection.

Severity of infection The degree or extent to which a microorganism multiplies or develops in a susceptible host. Severity of infection does not necessarily determine severity of illness.

Subclinical infection Infection associated with no detectable clinical signs but caused by a microorganism capable of producing clinical illness. Infection may remain subclinical, or signs and symptoms of disease may subsequently become apparent.

Susceptibility The extent to which a host is vulnerable to infection by a pathogen, taking into account a host's intrinsic and/or acquired traits that modify the risk of infection.

Tolerance (of pathogens to control) The ability of a microorganism to withstand specific environmental control measures (e.g., irradiation, temperature extremes, biocides, disinfection).

Tools (of microbial risk assessment) Techniques for conducting microbial risk assessment, which can be classified into three groups: qualitative, semiquantitative, and quantitative.

Uncertainty Ambiguity in microbial risk assessment arising from lack of knowledge about specific factors, parameters, or models.

Variability Observed differences attributable to true heterogeneity or diversity in a population or exposure parameter. Variability in microbial risk assessment cannot be reduced but only more precisely characterized.

Virulence The degree of intensity of the disease produced by a microorganism as indicated by its ability to invade the tissues of a host and the ensuing severity of illness.

Waterborne pathogen A microorganism capable of causing disease that may be transmitted via water and acquired through ingestion, bathing, or by other means.

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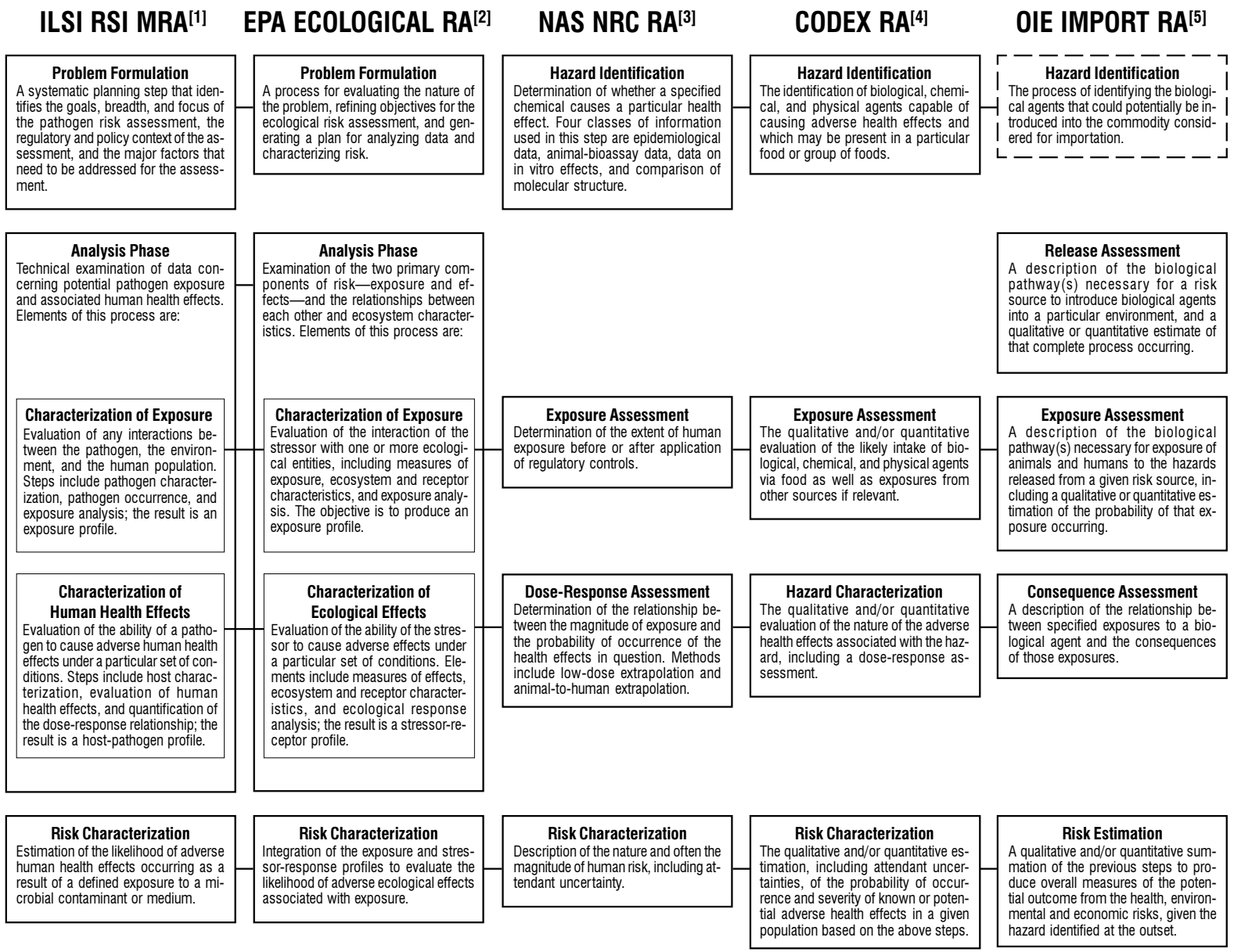
5. TABLE OF SYNONYMOUS TERMS IN RISK ASSESSMENT



Horizontal lines link synonymous terms between the various risk assessment frameworks.

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