Foundations and Frameworks for Human Microbial Risk Assessment

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ABSTRACT

Risk assessment is one part of a comprehensive risk management process, known as risk analysis. The risk characterization step within microbial risk assessment (MRA) serves as the bridge between risk assessment and risk management. Although a variety of MRA approaches are in use, limited analyses of MRA frameworks or their underlying principles and concepts exist. Organizations' desires to develop a unified MRA approach have been tempered by the realization that flexibility is essential for addressing various legislated mandates and regulations and for meeting diverse field application needs. This paper was developed to help EPA's Risk Assessment Forum, Microbial Risk Assessment Working Group to obtain new knowledge and insights about the nature and characteristics of available MRA frameworks and applications. This report includes a review of recent MRA policies and guidelines and a comparative analysis of 13 MRAs conducted or sponsored by governments worldwide. Two forms of risk assessment—chemical risk assessment and ecological risk assessment—provide the foundations for MRA as it was practiced at the time of this review. The National Academy's widely used four-step risk assessment paradigm is the prevailing context from which many modelers have approached microbial risk assessment. The most commonly cited underlying principles for MRA include: make public health protection the priority, base MRA on sound science, ensure transparency, use a structured and consistent approach, and allow for iterations. The dynamic aspects of pathogens, environmental processes, human populations, and the interrelationships of these entities are increasingly being noted as important MRA modeling issues. Four fundamental types of MRA frameworks were found: chemical risk assessment modified chemical risk assessment, problem definition followed by chemical risk assessment, and the International Life Sciences Institute (ILSI) framework. No agency has applied the ILSI framework in a complete MRA. Organizations use the chemical risk assessment paradigm for different purposes and work through the components in a variety of sequences and depths, tailoring the process to meet their needs. Few MRAs include problem formulation, but most

include a problem statement or definition. Some organizations have developed modules (self-contained mathematical models) to represent parts of the source-to-health effects chain. Further, the report describes environmental media-specific issues and approaches. Recommendations are made for advancing MRA through systems methodologies and communication strategies.

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LIST OF ABBREVIATIONS AND ACRONYMS

CDC	U.S. Centers for Disease Control and Prevention
CFSAN	Center for Food Standards and Nutrition (U.S. FDA)
Codex	Codex Alimentarius Commission
DALY	disability adjusted life year
ECFS	European Commission on Food Safety
EFSA	European Food Safety Authority
EPA	U.S. Environmental Protection Agency
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FDA	U.S. Food and Drug Administration
FSIS	Food Safety and Inspection Service (USDA)
HACCP	hazard analysis and critical control point
HSPD	Homeland Security Presidential Directives
ILSI	International Life Sciences Institute
IRAC	Interagency Risk Assessment Consortium
IRGC	International Risk Governance Council
JEMRA	Joint FAO/WHO Expert Meetings on Microbial Risk Assessment
LT2	Long Term 2 Enhanced Surface Water Treatment Rule
MRA	microbial risk assessment
NCEA	National Center for Environmental Assessment (U.S. EPA)
NHMRC	National Health and Medical Research Council (Australia)
NRC	National Research Council
NRMMC	Natural Resource Management Ministerial Council (Australia)
NZFSA	New Zealand Food Safety Authority
P/C	U.S. Presidential/Congressional Commission
SPS Agreement	Agreement on the Application of Sanitary and Phytosanitary Measures
UN	United Nations
USDA	U.S. Department of Agriculture
WHO	World Health Organization

PREFACE

Although risk assessments have been conducted for decades, government-sponsored conduct of microbial risk assessments (MRA) is a relatively new endeavor. Expanded computing and software capabilities now permit dynamic modeling of complex systems, such as those involved with human health effects associated with environmental exposures to microbial pathogens; thereby stimulating new approaches and methods for modeling MRA components. Further, new regulatory mandates and concerns about international trade have led to efforts worldwide for advancing MRA and harmonizing approaches. The Microbial Risk Assessment Working Group of EPA's Risk Assessment Forum has undertaken activities for evaluating and advancing MRA principles, policies, approaches, practices and methods.

This report was prepared under contract between EPA and The George Washington University (Contract #EP07H000172) to support the efforts of the Working Group by creating new knowledge about MRA foundations and frameworks used worldwide. Peer-reviewed literature, online government documents and MRAs, and materials presented at professional meetings served as crucial resources for the reviews and analyses presented in this report. The literature searches were completed in March 2007. Earlier drafts of this report were reviewed by EPA staff and external experts; the author gratefully acknowledges that the final report was improved by their insights and suggestions.

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EXECUTIVE SUMMARY

In the past decade, concerns about microbial contaminants in food, water, human and animal waste, and sources of bioterrorism have grown, giving rise to several initiatives to advance microbial risk assessment (MRA), which is one tool for identifying and ultimately reducing these hazards. Simultaneously, concerns were growing about the safety of foods in international trade, the various methods for assessing foodborne hazards, and the need for more scientific rigor and transparency in decision-making. The anthrax attacks in the United States, the emergence of severe acute respiratory syndrome, and avian flu outbreaks have added further urgency to developing microbial risk assessment methodologies. The massive flooding of New Orleans after Hurricane Katrina in 2005 highlighted the need for crisis applications of MRA.

Risk assessment is only one part of a comprehensive risk management process, known as risk analysis (EPA, 2005). The risk characterization step of MRA serves as the bridge between risk assessment and risk management activities (Nichols et al., 2005). Although various approaches are in use, limited analysis of MRA frameworks or their underlying principles and concepts exist.

Statement of Purpose

This paper was developed to help the U.S. Environmental Protection Agency's (EPA) Risk Assessment Forum, Microbial Risk Assessment Working Group to obtain new knowledge and insights about the nature and characteristics of available MRA frameworks and applications. The purposes of this paper are to

- Identify the underlying approaches, societal forces, principles and concepts that shape MRA frameworks
- Describe existing MRA frameworks
- Compare recently completed MRAs
- Discuss issues that arise when microbial pathogen risks are assessed for different environmental media

The scope of this paper includes recent MRA policies and MRAs that were either conducted or sponsored by governments worldwide.

Foundations of Microbial Risk Assessment Frameworks

Two forms of risk assessment, chemical risk assessment and ecological risk assessment provided the foundations for MRA as it was practiced at the time of this review. The four-step model—involving hazard identification, dose-response, exposure assessment, and risk characterization—has been used extensively (NRC, 1983). As a result, the chemical risk assessment framework was the prevailing context that many modelers used when approaching microbial risk assessment.

As the MRA field evolved, scientists recognized that terms were being used inconsistently to describe MRA concepts, and that frameworks and their underlying principles were diverging as well; a need for harmonizing terms and methods was apparent. The desire to develop a unified MRA approach has been tempered, however, by the realization that flexibility is essential for addressing legislated mandates and regulations. Forces affecting the development of microbial risk assessment frameworks include laws, regulations, guidelines, disease outbreaks, international conflicts over food safety requirements, scientific publications and debates, and the need for consistency and transparency. This paper reviews regulations, political and programmatic forces, as well as technical drivers found in international, European, North American, Australian, and New Zealand documents.

Guiding Principles and Concepts

Guidelines for MRA often include statements of principles and descriptions of conceptual issues to be considered when assessing the impacts of microbial pathogens. The majority of MRA guidelines and frameworks include fundamental principles and best practices for guiding the conduct of MRAs. Drawing from a wide range of documents, the most commonly found principles for MRA were

- Make health protection the priority.
- Conduct processes based on sound science, weighing the evidence.
- Ensure transparency through mechanisms such as open processes and clear documentation.
- Use and document structured, consistent processes.
- Provide flexible guidelines, not rigid requirements.

- Keep risk assessment and risk management functionally separate, while allowing for ongoing, transparent, and appropriate opportunities for information exchange.
- Ensure clear, concrete, and specific questions early in the process.
- Clarify assumptions and uncertainties.
- Permit iterations of the process, allowing new information to be used and the assessment to be updated.
- Provide outputs relevant and useful to decision-makers.

One of the most important principles—transparency—typically refers to two issues: 1) documentation of methods, models, sources of data, assumptions and uncertainties, and 2) open decision-making processes.

Some of the overarching concepts most often mentioned in MRA policy documents and peer-reviewed literature include

- Consider the dynamic dimensions of the pathogen, environment, host, and human population.
- Construct a conceptual model early in the process.
- Model realistic conditions.
- Use a comprehensive source-to-exposure pathway paradigm to organize information and construct a series of linked mathematical models.
- Recognize the interrelated nature of steps in the paradigm, such as the sequence and timing of events.
- Clearly define terms including “infection” and health outcomes.
- Clearly define the outcome metrics (individual and/or population scale), and ensure that they link to the decision-makers’ needs.

Two dominant types of MRA are risk-ranking exercises and product pathogen pathway analyses. Many issues in MRA differ importantly from chemical risk assessment, demanding different conceptual and practical modeling approaches (WHO, 2005; Schaub, 2004; FAO/WHO, 2003a; OECD/WHO, 2003; Eisenberg et al., 2002; Parkin, 2002; Medical Research Council Institute for Environment and Health, 2000; ILSI, 2000; Haas et al., 1999; ECFS, 1997).

The unique characteristics of microorganisms and host populations and their dynamic aspects are be considered carefully when designing an MRA approach (Buchanan, 2003).

Microbial Risk Assessment Frameworks

Currently, four fundamental types of microbial risk assessment frameworks exist. One type uses the chemical risk assessment framework described in section 2.1.1. (NRC, 1983); another type uses a modified NRC framework, in which the two middle steps are sometimes reversed; a third framework builds on the NRC approach by adding a problem definition step (e.g., part of planning and scoping, or problem formulation) (U.S. EPA, 2005a, 2004b, 1989); and the final type of framework was developed by ILSI (2000).

Although the NRC (1983) framework is the most commonly used framework, it is not used consistently; no agency has yet applied the ILSI model for a final risk assessment. Some agencies include MRA as part of a risk management paradigm, but very few have discussed risk communication as a consideration in MRA processes.

Comparison of Frameworks

To elucidate the similarities and differences between governments' and agencies' MRA approaches, this review includes the most recently completed and available MRA for each nation or agency, when there was more than one completed MRA per government, and evaluates the type of MRA framework used and the components included in the framework. MRAs were found for pathogens in air, drinking water, recreational water, foods (both fresh and processed), biosolids, modified organisms, and intentional uses of microbes.

The analytic focus of this project centered on 12 recently published, government-sponsored MRAs, and one series of EPA MRAs—for biopesticides, yielding 13 approaches. The MRAs compared for this project were

- Cryptosporidium in drinking water (WHO, 2006a)
- Cryptosporidium in drinking water in France (Pouillot et al., 2004)
- Salmonella (non-typhoidal) in poultry (whole and pieces) in New Zealand (NZFSA, 2004)
- *S. enteriditis* in shell eggs and egg products in the United States (USDA, 2005b)
- *S. typhimurium* in three sets of pig-meat products in the United Kingdom (Hill et al. 2003)

- *V. vulnificus* in raw oysters (WHO, 2005)
- *V. parahaemolyticus* in raw oysters in the United States (U.S. FDA, 2005)
- Campylobacter in broiler meat in The Netherlands (Nauta et al., 2005)
- *L. monocytogenes* in fish in Sweden (Lindqvist and Westöö, 2000)
- Eight microbial pathogens in processed wild game in the United Kingdom (Coburn et al., 2005)
- Ochratoxin A in foods (EFSA, 2006c)
- The MRA portion of the economic analysis for the final Long Term 2 Enhanced Surface Water Rule (EPA, 2005b)

An example of the U.S. biopesticides series is

- *Streptomyces lydicus* WYEC 108 (U.S. EPA, 2004a)

Microbial risk assessments involve many factors and complex relationships, including the dynamic aspects of pathogens and hosts and their environment. Tools such as risk assessment frameworks and modules help risk assessors organize the complex microbial risk conditions and model dynamic relationships. MRA frameworks provide a broad template to guide the organization of many factors into a series of technical steps and to identify data gaps and appropriate computational methods.

The most basic decision-making model has been described by Drucker (2001) as including three phases: problem definition, analysis, and interpretation. Two of these three components are apparent in both the chemical and microbial risk assessment paradigms; the phase that clearly receives the least attention in MRA frameworks is problem definition. Most MRAs do not acknowledge problem formulation (or "problem definition") as a step in the assessment process, but do have a section that states the purpose of the assessment and/or describes the problem.

The MRAs in this paper handled scoping issues in different ways—in statements of purpose, risk profiles, or problem formulation steps. The 13 MRAs typically had a national scope, but few addressed place and time explicitly. The scope of most MRAs conducted to date has focused on specific places (e.g., Soller et al., 2003), foods (e.g., U.S. FDA, 2005), or pathogens in a limited number of foods (e.g., USDA, 2005b). Among the 13 MRAs, all but one

focused on a specific pathogen. Several MRAs investigated the impacts of a variety of environmental conditions (e.g., U.S. FDA, 2005) or a variety of foods (e.g., Coburn et al., 2005; USDA, 2005a).

Most organizations that have published MRAs have used the traditional chemical risk assessment paradigm (NRC, 1983). For food-related MRAs, organizations tend to use a modification of this framework (e.g., U.S. FDA, 2003a; WHO, 2002). In a drinking water risk assessment, WHO (2006a) modified the traditional NRC steps in a unique manner: problem formulation was documented after hazard identification. The EPA National Homeland Security Research Center office has used the ILSI (2000) paradigm as the basis for its incident response assessments (Nichols et al., 2006).

A comparison of the traditional risk assessment steps yielded the following observations: among the MRAs reviewed, the hazard identification step showed the least variation in content; all MRAs described host characteristics and disease outcomes and modeled the dose-response pathogen-host relationship in the hazard characterization (or dose-response) step; in 10 of the MRAs, the exposure assessment step was the most extensively documented. Risk assessors used this step to effectively identify and model the complexity of the pathogen pathway and routes of exposure and to describe their modeling approaches and outputs. Although levels of detail differ, all agencies used the risk characterization step to present, describe, and interpret their modeling results. Most MRAs also evaluated and described the sources of uncertainty and variability that affected the final MRA estimate.

While the frameworks used in the 13 MRAs were quite similar (some form of problem description precede the four traditional risk assessment steps), they differed in the implementation and depth of the framework components. The ability to conduct an effective MRA may be constrained by several factors, including the lack of skilled personnel to fully implement the analytic steps. Important gaps in knowledge about disease processes and microbial pathogen lifecycles require assumptions and uncertainty analysis (Parkin, 2002). An incomplete understanding of source-pathway-receptor elements and linkages also limits the conduct of MRAs (Godfrey and Smith, 2005).

A recent and key contribution to MRA is the development of a modular approach, particularly to exposure assessments' pathway analyses. Currently, the extent of missing or insufficient data is much greater in most MRAs than in chemical risk assessments, resulting in a greater degree of uncertainty. Additionally, the extent to which MRA components vary is largely

unknown; the value of conducting sensitivity and probabilistic analyses to reveal the impacts of variations in MRA components cannot be overestimated.

Environmental Media and Microbial Risk Assessment

Issues related to pathogens in specific environmental media have been identified in various MRAs. Media-specific factors and characteristics are important to pathogen survival, persistence, growth, and die-off. The significance of having a comprehensive organizational structure and components to characterize the pathogen's progress from source to host is key. Each environmental medium or matrix entails different challenges and opportunities for pathogens. It is easy for assessors to miss important factors in such complex conditions without the benefit of a conceptual model and systematic framework to guide the consideration of the many factors and their inter-relationships. These pathways are complex, requiring detailed compilation of concepts and data to adequately inform and conduct MRAs. Furthermore, translation of the factors and relationships into tractable formulas requires technical skill and attention to detail.

Developing broad, flexible categories of MRA elements is an important goal in module development. It is recommended that modules not be rigid lists of steps or elements to consider in every MRA, but could be groupings of characteristics to be considered in specific risk assessments, thereby serving as guides for risk assessors to assure that complete and effective MRAs are implemented. Modules produce more transparent organization and greater description of the many factors that contribute to pathogen-related health risks. Modules can be constructed to assure that they align with functional components of the pathogen's pathway and facilitate the design and conduct of mathematical models.

Recommendations

Although similarities exist among many microbial risk assessment frameworks, the differences may result in important variations in MRA results. Beginning with effective planning and scoping, problem formulation, definitions, and a sound conceptual model are essential to conducting a meaningful and relevant risk assessment. Getting the questions right early in the process through dialogue with risk managers is a crucial step. Developing a sound and comprehensive conceptual model may require several iterations, but identifying the fundamental components of the model should be done early, so the model will focus on risk managers' needs.

Furthermore, agencies responsible for specific types of MRAs (e.g., food, water) may be able to identify modules that they will commonly need for the MRAs within their authorities. A large number of the elements required for each module could be listed and organized in advance, and the elements could be further refined when specific applications are defined.

With comprehensive paradigms to help risk assessors identify and consider the many potential factors involved in pathogen-related illness, MRAs will become increasingly informative and contribute to more effective public health interventions.

1. INTRODUCTION[1]

1.1. BACKGROUND

The public health significance of microbial pathogen-related disease is widely known and confirmed by public health data. The U.S. Centers for Disease Control and Prevention (CDC) has estimated that annually in the United States, there are 76 million foodborne illnesses, 325,000 hospitalizations and 5,000 deaths (Mead et al., 1999). The World Health Organization (WHO) has estimated that, worldwide, contaminated drinking water causes 1.8 million deaths and disables tens of millions more people each year (WHO, 2004a). The United Nations has identified water as a basic human right and has asserted that providing safe water is a clear responsibility of governments. However, nearly a billion people worldwide remain without ready access to safe water (Davison et al., 2005). In the past decade, concerns about microbial contaminants in food and water from human and animal waste and from sources of bioterrorism have grown, giving rise to several initiatives to advance microbial risk assessment (MRA), which is one tool for identifying and ultimately reducing these hazards.

1.1.1. Historical Perspective

People have been concerned about reducing disease risks since prehistoric times; the earliest known rational framework[2] for addressing these risks was used in ancient Greece (Rosen, 1993). Although scientists recognized microorganisms as disease agents in the mid-nineteenth century, many of the remedial actions taken to control these agents during the subsequent Sanitary Reform Movement were motivated more by beliefs than by scientific knowledge (Webster, 1993; Rosen, 1993; Walker, 1968). In the twentieth century, the United States developed federal laws and government agencies to address contaminants in food and water. First, the U.S. Food and Drug Administration (FDA) was established in 1906 and mandated by the Federal Food, Drug, and Cosmetics Act of 1938 (U.S. FDA, 1938) to implement the first health-based standard of protection. As a result of this and other legislation, essential concepts and methods evolved for quantifying and controlling contaminant-related health risks in food, water, and other media (Hutt, 1997).

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[1]Dr. Parkin is a Professor of Environmental and Occupational Health in the School of Public Health and Health Services of The George Washington University Medical Center in Washington, DC. Portions of this report have been drawn from Parkin R. "Microbial Risk Assessment" in Robson MG, Toscano WA (eds.) 2007. Risk assessment for environmental health. Washington, DC: Jossey-Bass.

[2]Framework is defined as "an integrated, holistic and structured approach … by which we can investigate risk issues and the governance processes and structures pertaining to them" (IRGC, 2005).

Second, the U.S. Public Health Service and later the U.S. Environmental Protection Agency (EPA) developed drinking water standards, in part, to control microbial pathogen hazards. From the 1970s, EPA and the CDC used increasingly systematic and quantitative ways for addressing human health hazards. Methods were improved to detect and classify pathogens, identify sources of pathogens, and conduct public health surveillance. Methods developed by EPA for estimating environmentally related human health risks required new data, such as the population's consumption rates of various foods and water. In response, FDA collected consumption data and defined protocols for assessing health effects (Hutt, 1997; Rhomberg, 1995).

As EPA, FDA, and other agencies became more involved in risk assessment, the needs emerged for estimating risks at unmeasurable exposure levels, organizing diverging risk assessment concepts and approaches, and establishing determinations of safety before products were allowed onto the market. The National Research Council (NRC) addressed these needs by publishing a risk assessment paradigm that remains in wide use today (NRC, 1983). However, the framework was designed for addressing chemical carcinogens, which were the foodborne and environmental health risks of concern at that time.

An early MRA approach was proposed in the 1970s (Mossel and Drion, 1979), and Haas (1983) proposed methods for dose-response relationships. Others explored dose-response relationships to address pathogens in drinking water (Regli et al., 1991; Rose et al., 1991), and EPA used these studies as the basis to choose an acceptable level for the risk of infection (1 case/10,000 people/year) (Regli et al., 1991). However, little advancement of MRA occurred until the 1990s.

In 1992, the United Kingdom Health and Safety Executive organized a conference that in part considered human health risks associated with food- and water-borne pathogens, and genetically modified organisms. In 1993, not only did the U.S. National Advisory Committee on Microbial Criteria for Food establish a working group to study microbial risk assessment, but also the International Life Sciences Institute of Europe convened a workshop to identify the scientific bases for MRA (ACDP, 1996).

The importance of advancing microbial risk assessment became even more apparent following the 1993 cryptosporidiosis outbreak in Milwaukee, which was linked to the city's drinking water supply. Researchers have estimated that thousands of people were hospitalized and over 100 died (Griffin et al. 1998; Kramer et al., 1996; MacKenzie et al., 1994). This outbreak motivated legislators to take action for public health protection. With the passage of

the 1996 Amendments to the Safe Drinking Water Act and the Food Quality Protection Act, EPA's and FDA's attention to microbial risk assessment became even more critical (U.S. FDA, 1996; U.S. 104th Congress, 1996).

Simultaneously, concerns were growing about the safety of foods in international trade, the various methods for assessing foodborne hazards, and the need for more scientific rigor, and transparency in decision-making. The Codex Alimentarius Commission (Codex) developed guidelines for practicing risk assessment for food products, and in 1993, adopted the Hazard Assessment-Critical Control Point (HACCP) system to protect the global food supply (WHO, 2006b).

The 2001 anthrax attacks in the United States, the emergence of severe acute respiratory syndrome, and avian flu outbreaks have added further urgency to developing microbial risk assessment methodologies. The massive flooding of New Orleans after Hurricane Katrina in 2005 highlighted the need for crisis applications of MRA. Clearly, there are ever-increasing reasons to advance microbial risk assessment frameworks that can also be used to rapidly assess, characterize, and address pathogen hazards in a tiered approach, and to communicate the hazards effectively to decision-makers and the public.

1.1.2. Origin of the Document

Risk assessment is only one part of a comprehensive risk management process (Jardine et al., 2003), known as risk analysis (U.S. EPA, 2005a). The risk characterization step of MRA serves as the bridge between risk assessment and risk management activities. The risk management context is very important in shaping the scope and focus of the MRA, while the results of the assessment are crucial for sound decision-making about actions to reduce human health risks effectively.

Through its recent deliberations, the Interagency Risk Assessment Consortium has identified the need to harmonize and advance MRA methodologies (IRAC-MRAF, 2002). Although various approaches are in use, limited analyses of MRA frameworks or their underlying principles and concepts exist. The desire to develop a unified MRA approach has been tempered, however, by the realization that flexibility is essential for addressing legislated mandates and regulations that apply to a variety of both environmental media and microbial pathogens.

This paper was developed to assist EPA's Risk Assessment Forum—Microbial Risk Assessment Working Group in obtaining new knowledge and insights about the nature and

characteristics of available MRA frameworks and applications. The structure of this document was prepared in consultation with the professional staff of EPA's Office of Water.

1.2. STATEMENT OF PURPOSE

The goal of risk assessment is to estimate the probability of possible consequences due to exposure to specific risk agents. However, risk issues are fraught with complexity, uncertainty, and ambiguity. Many organizations have developed comprehensive, consistent, and yet flexible frameworks for systematically applying analytical methods and generating risk estimates (IRGC, 2005).

Asano and colleagues (2007) have described microbial risk assessment as "The process that is used to evaluate the likelihood of adverse human health effects that can occur following exposure to pathogenic microorganisms or to a medium in which pathogens occur. …the MRA process includes evaluation and consideration of quantitative information; however, qualitative information is also employed as appropriate…."

The purposes of this paper are to

- Identify the underlying approaches, societal forces, principles and concepts that shape MRA frameworks
- Describe existing MRA framework
- Compare recently completed MRAs
- Discuss issues that arise when microbial pathogen risks are assessed for different environmental media

The scope of this paper includes recent MRA policies and MRAs that were either conducted or sponsored by governments. The most recently completed MRA available for a government agency was selected for this study. Online tools (Google Scholar, Scopus, etc.), traditional literature search methods (interlibrary loans) and personal communications with professional risk assessors were used to search for policies and completed MRAs. The United Nations (FAO and WHO), the European Union, and several nations were found to have policies describing approaches for assessing and managing microbial pathogen risks. MRAs were found for several nations in Europe and North America, New Zealand, the European Union and the United Nations. A total of 13 MRAs are presented and compared in this review.

2. FOUNDATIONS OF MICROBIAL RISK ASSESSMENT FRAMEWORKS

Decision support tools or frameworks are used to rank issues, prioritize needs, and allocate resources. All of these functions can be met using stepwise risk assessment approaches, but all rely on the availability of sufficient knowledge, data, methods, and analytic tools. The thoroughness of a risk assessment relies on its objectives and the data available. However, the very broad and generic steps for conducting risk assessment—problem definition, data collection and analysis, and interpretation—depend on neither specific purposes nor data.

Governmental agencies in North America, Europe, and other areas have published microbial risk assessment frameworks; other organizations have applied approaches for pathogen-specific MRAs without publishing explicit frameworks.

The purpose of this section is to identify the societal forces that have contributed to the development of MRA frameworks and describe the two fundamental frameworks that have been the primary, essential inputs to existing MRA approaches and applications.

2.1. UNDERLYING FORMS OF RISK ASSESSMENT

Two forms of risk assessment—the chemical risk assessment paradigm and ecological risk assessment—provide the foundations for MRA as it was practiced at the time of this review.

2.1.1. Chemical Risk Assessment

Chemicals in foods were first addressed in a public policy framework in the mid-1800s, when they were viewed as adulterants. In the early twentieth century, chemicals were considered food safety and poisoning issues; these chemicals were later regulated as if a "safe threshold" existed, below which people could be exposed to chemicals without harm (Hutt, 1997; NRC, 1983). As animal testing produced more data, the underlying assumptions used to estimate chemical risks came under question and led to intense debates. One result of these tensions was the publication of the National Research Council's (NRC) "Red Book" (NRC, 1983). This document codified the approach to assess chemical risks and described the state of knowledge and underlying assumptions for the method.

The four-step model—involving hazard identification, dose-response, exposure assessment, and risk characterization[3]—was used extensively in the following decades (see

[3] The following definitions have been derived from the materials presented in U.S. EPA, 2005a:

- Hazard identification is used to determine whether a microbial pathogen can cause adverse health effects in humans and what those effects might be.

Figure 1). As a result, the chemical risk assessment framework was the prevailing context from which many modelers approached microbial risk assessment.

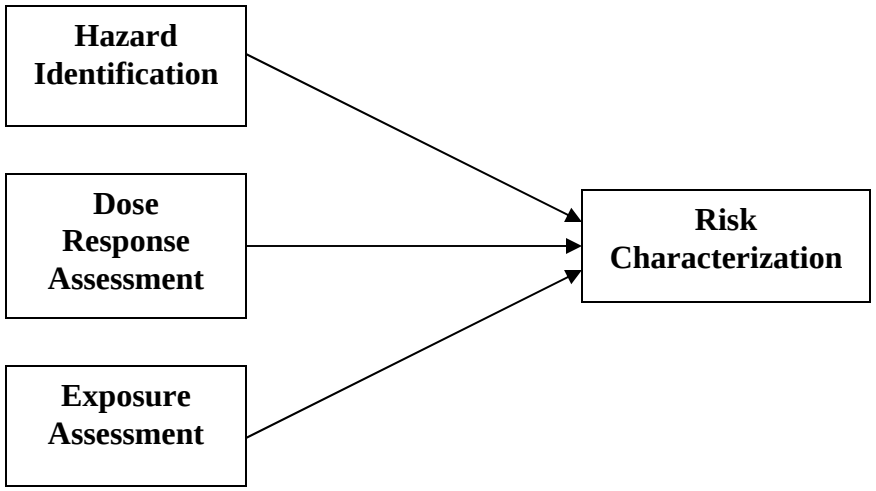


Figure 1. Steps in the traditional risk assessment framework.
Source: Adapted from NRC, 1983

In the early 1990s, several risk assessors applied the chemical risk assessment paradigm to microbial pathogen issues. However, each set of investigators identified problems with using this framework (Haas et al., 1993; Sobsey et al., 1993; Regli et al., 1991; Rose et al., 1991), and other researchers have identified additional issues since then (e.g., Eisenberg et al., 2006; Eisenberg et al., 2002). As Eisenberg et al. (2006) pointed out, MRA is fundamentally different from chemical risk assessment; most importantly, infectious disease processes (including infectivity and incubation periods, etc.) and immunity are key issues not considered in chemical risk assessment. Further, chemical risk assessment relies on static modeling techniques, which cannot represent dynamic processes such as disease transmission, and on the assumption that each exposure is an independent event. Infection is a function of dose and, rather than mortality, may be the health outcome of concern. In MRA, the population is separated into the immune and

- Dose-response is the quantitative relationship between an exposure and the extent of disease produced. Dose-relationship is often one component of hazard characterization.
- Exposure assessment is the step used to identify the pathways by which pathogens may reach individuals, estimate the extent of pathogen exposure among humans, and estimate the likely number of persons exposed.
- Hazard characterization is a description of the potential adverse health effects attributable to a specific pathogen, the mechanisms by which it exerts its effects, and the associated dose, route, duration, and timing of exposure.
- Risk characterization is the integration of information about the hazard, exposure, and dose-response, and the estimation of the likelihood of adverse health effects among exposed individuals. Descriptions of the modeling assumptions, uncertainties and variability, along with possible risk management options are also included in this step.

susceptible subpopulations to effectively estimate risk. When secondary transmission is involved, dynamic modeling and population scale measures of risk are crucial (Eisenberg et al., 2006).

Some of the problems that researchers have identified as not being addressed by the "Red Book" paradigm for microorganisms include

- Microorganisms can grow, evolve into different life stages, and die off.
- Virulence varies during a pathogen's life cycle and between different pathogen strains.
- Pathogens behave differently under different temperature and time conditions (e.g., in food processing and preparation), as well as in different media and matrices (e.g., water vs. food, and different types of foods and soils).
- Microbial pathogens are not evenly distributed in the environment, and may be found in clumps, which present very uneven probabilities of exposure.
- Secondary or person-to-person transmission occurs in many infectious disease processes, while chemical exposure assessment occurs in the individual.
- Attack rates and infection rates differ and asymptomatic carriers exist.
- Multiple, independent exposures occur as part of the infectious disease process.

Although the microbial risk assessment steps are often the same as for chemical risk assessments, the emphasis, elements, and conduct are different in various stages of MRAs due to the dynamic natures of the agent and population (ECFS, 1997). In particular, changes in the population's immunity and susceptibility status are not considered in the traditional risk assessment paradigm or in chemical risk assessments themselves.

2.1.2. Ecological Risk Assessment

During the 1980s and early 1990s, ecological risk assessment evolved at EPA (U.S. EPA, 1992). Although ecologic modelers were informed by the chemical risk assessment approach, they recognized that as a paradigm, it did not entirely fit their needs. Ecological risk assessment demands a comprehensive, systems-oriented context, which requires modelers with different backgrounds and training. As a result, a lack of a clearly defined problem statement makes ecological risk assessments difficult and inefficient. Because the Red Book did not include a

problem formulation[4] step, ecological risk assessors created one and explained how to implement it (U.S. EPA, 1992).

The three primary steps in ecological risk assessment frameworks used in North America are problem formulation, analysis, and risk characterization (U.S. EPA, 1998; Environment Canada, 1996). The middle step involves characterizations of exposures and effects (see Figure 2). Ecological risk assessors' work contributed valuable insights for advancing microbial risk assessment concepts and methods, such as interactions between agents (which may include microbial pathogens) and hosts that are living entities with several life stages.

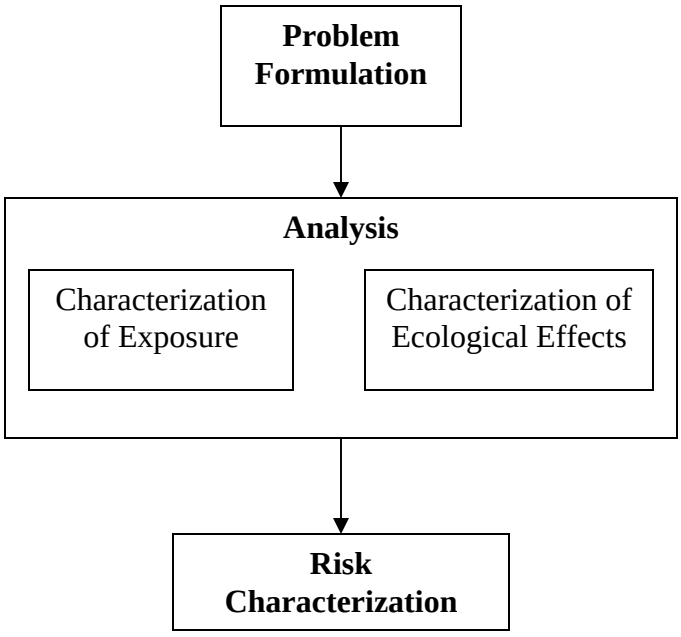


Figure 2. Components of ecological risk assessment.
Source: Adapted from Jardine et al., 2003

2.2. FORCES AFFECTING MICROBIAL RISK ASSESSMENT

Forces that have affected the development of microbial risk assessment frameworks include laws, regulations, guidelines, disease outbreaks, international conflicts over food safety requirements, scientific publications and debates, and the need for consistency and transparency. Underlying all of these drivers, however, was a growing awareness that natural and manmade microbial pathogens are potentially very harmful to humans and the environment and thus merited more rigorous risk assessment and management strategies. As the MRA field evolved,

[4] Problem formulation was first used in EPA's ecological risk assessment framework (U.S. EPA, 1992). This refers to the initial systematic planning step in which the purpose of the assessment is stated, goals and objectives are defined, the endpoints and conceptual model for the assessment are described, major factors and data needs are recognized, and the contexts for the assessment are presented (U.S. EPA, 2005a; EPA, 2004b).

scientists recognized that terms were being used inconsistently to describe MRA concepts, and that frameworks and their underlying principles were diverging as well; a need for harmonizing terms and methods became apparent. Furthermore, the public and officials were increasingly expressing concerns, seeking more scientifically sound processes to control microbial risks, and looking for assurances that limited resources were being used to address the risks effectively.

2.2.1. Regulatory Forces

2.2.1.1. *United States*

Laws and regulations, an Executive Order, and Agency Directives have influenced the development of MRA policies and approaches in the United States. The agencies primarily affected have been EPA, FDA, and the U.S. Department of Agriculture (USDA). A summary of these agency-related regulatory forces follows.

2.2.1.1.1. *Environmental Protection Agency*. The 1996 Amendments to the Safe Drinking Water Act required EPA to list unregulated microbial pathogens known or expected to occur in public water systems and that may require regulation; the Contaminant Candidate List including microbial pathogens was issued in 1998 and updated in 2005. To obtain evidence about pathogen occurrence, the Information Collection Rule was promulgated in 1996; it required water utilities serving over 10,000 people to test source and finished water monthly. Further, the Long Term 2 Enhanced Surface Water Treatment Rule (LT2) required health-based approaches for establishing new rules to reduce microbial pathogen hazards associated with drinking water (U.S. EPA, 2005b). The intent of the LT2 rule was to supplement microbial pathogen treatment requirements where greater public health protection is necessary; the primary pathogen concern was cryptosporidium. The rule also considered the tradeoffs of controlling both pathogen and disinfection byproduct risks. Concerns about the potential hazards associated with microbial products of biotechnology were raised in the 1980s, causing EPA to evaluate its existing regulations and determine that the agency had the power to regulate such hazards. Since 1986, EPA has been reviewing notices on new microorganisms under section 5 of the Toxic Substances Control Act. To implement notification procedures specific for microorganisms, EPA promulgated an additional rule in 1997 (U.S. EPA, 1997).

EPA promulgated the Part 503 Rule in 1993 to set standards for the use and disposal of biosolids, but—unlike for chemical pollutants—pathogen limits were not based on risk

assessment but on performance, technological or other bases (Eisenberg et al., 2006). More recently, in response to Homeland Security Presidential Directives HSPD-7, 9, and 10 (Nichols et al., 2006), EPA has begun to conduct MRAs related to bioagents that may be used intentionally to harm populations. The Presidential Directives required EPA to

- Be the sector-specific lead agency for critical water infrastructure safety and security (HSPD-7)
- Create a fully coordinated surveillance and monitoring program for early detection of bioagents (HSPD-9)
- Develop a nationwide laboratory network to support routine monitoring and response requirements (HSPD-9)
- Serve as the nation's lead agency in decontamination efforts (HSPD-10)

2.2.1.1.2. ***Food and Drug Administration***. The FDA derives its food safety authorities from the Federal Food, Drug, and Cosmetics Act of 1938 (FDCA), which defined the conditions for "adulterated" food. The agency is responsible for regulating the safety of all foods, substances intentionally added to food and used in food processing, and manmade and natural food contaminants. The scope of these authorities covers all activities between production and retail sale. Additional authorities were directed to FDA through the Food Additives Amendment of 1958. FDA carries out its food safety authorities through the Center for Food Safety and Applied Nutrition (CFSAN), which establishes policies and standards, manages the premarket approval program, and sets priorities for the field inspection and compliance force. These legal foundations are not explicitly stated in FDA's MRAs, but clearly give the agency authority to conduct MRAs for protecting the public from foodborne pathogens. The provisions of the Food Quality Protection Act of 1996 call for evaluations of the safety of potential contaminants in the food supply, particularly in reference to susceptible subpopulations such as infants and children. The review of toxicological data for assessing biopesticide safety in preparation for registration and use complies with the requirements of the Act. (e.g., U.S. EPA, 2004a).

2.2.1.1.3. ***U.S. Department of Agriculture.*** The USDA has statutory authority over meat, poultry, and processed egg products. This agency's authority derives from several acts: the Federal Meat Inspection Act, the Poultry Products Inspection Act, and the Egg Products

Inspection Act. Like the Food, Drugs, and Cosmetics Act, all of these acts define conditions for "adulterated." The USDA food safety program is primarily carried out by the Food Safety and Inspection Service (FSIS), which has rulemaking authority and establishes standards. In 1996, FSIS required all meat and poultry processing plants to adopt the hazard analysis and critical control point (HACCP) system. Like FDA, USDA does not explicitly state its legal authorities for conducting its MRAs. The Food Safety Commission was established in the USDA through enactment of the Farm Security and Rural Investment Act of 2002. This law mandated improvements to the food safety system, building on a National Academy of Sciences report that criticized the inefficiencies of the U.S. food safety system (IOM/NRC, 1998). These recommendations added incentives for the USDA to advance its MRA methodologies as a tool for improving the safety of food processes.

In 1997 and 1998, President Clinton announced the interagency Food Safety Initiative, proposed additional resources be dedicated to international food safety issues, and established the President's Council on Food Safety (Executive Order 13100, 1998). Federal agencies subsequently increased their attention to microbial risk assessment, and produced new MRA approaches (e.g., USDA, 2005b; U.S. FDA/CFSAN, 2005; ILSI, 2000).

2.2.1.2. *Canada*

The Federal-Provincial Subcommittee on Drinking Water (of the Federal-Provincial-Territorial Committee on Environmental and Occupational Health) developed Canada's *Guidelines for Canadian Drinking Water Quality*. These guidelines rely on the concepts that science-based assessments and flexible approaches are necessary to accommodate diverse needs across the nation (Health Canada, 2000; 1999a). No MRA completed and published by a government agency was found at the time of this project.

2.2.1.3. *United Kingdom*

The Food Standards Act of 1999 authorized the Food Standards Agency (Medical Research Council Institute for Environment and Health, 2000). The Agency focused its attention on developing methodologies for addressing microbial hazards.

2.2.1.4. *European Union*

The European Union (EU) has several legal bases relevant to microbial risk assessments. These regulations apply to the conduct of MRAs and serve as the basis for the EU's guidance for the risk assessment of genetically modified organisms (EFSA, 2005).

- The General Food Law (Regulation [EC] 178/2002) defines "risk assessment" and the general principles of food safety. It also describes the principles of food law and procedures for food safety, as well as the responsibilities of the European Food Safety Authority (EFSA). This regulation defines risk analysis, risk assessment (as the four traditional steps), risk management and risk communication (EFSA, 2006b).

- The regulation on genetically modified food and feed (EC Regulation 1829/2003) requires marketing decision-making to be based on scientific risk assessment conducted by the EFSA.

- European regulations for wild game meat (EC Regulation 853/2004) have motivated nations to characterize the risks in wild processed game to ensure the products can enter international trade routes (e.g., Hill et al., 2003).

- European Commission Regulation No. 466/2001 set maximum levels for certain contaminants in foods, which was amended by Regulation 123/2005. These were the regulations that mandated the Ochratoxin A in food toxicological review and opinion, issued in 2006 (EFSA, 2006c).

2.2.1.5. *United Nations*

Several key United Nations declarations have focused more attention on microbial hazards and resulted in the development of MRA principles and frameworks. Among these, several stand out in importance:

- The 1992 World Declaration and Plan of Action for Nutrition, adopted by the International Conference on Nutrition, explicitly stated that the protection of food is an essential responsibility of governments. In response, the Food and Agriculture Organization of the United Nations (FAO) and WHO were requested to involve all member countries in Codex activities, including MRA consultations (FAO/WHO, 1995).

- In 1995, the Uruguay Round of Trade Agreements' General Agreement on Tariffs and Trades and the subsequent *Agreement on the Application of Sanitary and Phytosanitary Measures* (or the SPS Agreement)[5] affirmed that no member should be

[5] This Agreement can be found at http://www.wto.org/English/tratop_e/sps_e/spsagr.htm. Last accessed on March 4, 2006.

prevented from adopting or enforcing measures needed to protect health (WTO, 1995). The SPS Agreement specifically cited Codex's standards, guidelines, and recommendations as reflections of international consensus about protecting human health from foodborne hazards. This international trade agreement required World Trade Organization members to conduct risk assessments for setting limits on health risks in foods. The SPS Agreement also served as the foundation for the Joint FAO/WHO Expert Consultation on Application of Risk Analysis to Food Standards Issues (WTO, 1995).

- The 1995 Agreement on Technical Barriers to Trade prompted more attention to addressing international food trade concerns, including microbial risks (FAO/WHO, 2002a; 1995). FAO and WHO conducted a series of expert consultations that have resulted in several reports to guide risk assessments of foodborne pathogens.[6] Building on these bases, Codex prepared principles and guidelines for MRA (Codex, 1999).

- The 2000 United Nations (UN) World Health Assembly food safety resolution called on members to recognize food safety as an essential public health function and develop systems to reduce the burden of foodborne disease. It also directed members to support its MRA advisory body (the Joint FAO/WHO Expert Meetings on Microbial Risk Assessment, or JEMRA), which conducts MRAs and provides expert advice to members.

2.2.2. Political and Programmatic Forces

2.2.2.1. *United States*

A number of policies and activities promulgated by U.S. agencies and other influential organizations affected the direction and development of risk assessment:

- A pivotal report of EPA's Science Advisory Board described efforts to rank order environmental hazards, and recommended funding levels in alignment with real, not perceived, risks for reducing risks more effectively (U.S. EPA, 1990). While this report did not have major effects on EPA's budget, it did stimulate extensive debate, which noted that microbial pathogens were largely ignored but significant hazards.

- Public concerns about the scientific integrity of risk assessments led Administrator Browner to issue a policy for risk characterization in March 1995. In her statement, she reaffirmed the principles and guidance issued by EPA in 1992, and asserted that risk assessments across the Agency must be transparent, clear, reasonable, and consistent agency-wide (See Appendix A in U.S. EPA, 2000a).

[6] These documents can be found at http://www.who.int/foodsafety/micro/en. Last accessed on March 4, 2006.

- Foodborne hazards have been addressed through the HACCP approach, which was developed through an intensive public-private sector process.

- In 1997 the interagency National Food Safety Initiative focused on reducing foodborne pathogen-related illness rates by improving farm-to-fork MRA methods, including dose-response modeling. The group recommended the use of risk assessment as one means for addressing food safety issues. The political and financial support that resulted from the Initiative's report helped improve microbial risk assessment and research capabilities (Dennis et al., 2001–2002).

- A 1998 Institute of Medicine/National Research Council report recommended basing food safety system reforms on sound science and risk assessment, and noted that risk assessment is an essential component in setting priorities and allocating resources effectively (Taylor et al., 2003; IOM/NRC, 1998).

- In response to three Homeland Security Presidential Directives (HSPD-7, 9, and 10), EPA established a comprehensive National Homeland Security Research Center. One of the Center's initiatives is the development of a microbial risk assessment framework. A preliminary approach for incident response to bioagents has been based on existing methodologies and is organized into three tiers: Site/Incident Assessment, Exposure and Hazard Assessments, and Risk Characterization (Nichols et al., 2006).

Throughout this period, agencies such as the EPA, FDA, and USDA were gaining experience with the concepts, models, and conduct of MRA. The agencies produced several interagency MRAs, which built capacity for conducting assessments across agency boundaries. Workshops were held to discuss key concepts, evaluate the work completed, and review lessons that should be shared and used to identify potential improvements.

2.2.2.2. *Canada*

Canada has also had a number of agencies and organizations whose activities and policies have had an impact on microbial risk assessment:

- Lammerding (2006) of the Public Health Agency of Canada has described risk assessment as "a structured, systematic approach to integrate and evaluate information…." and has presented the Codex (1999) four-compartment approach as appropriate for MRA.

- In 1999, Health Canada examined the presence and hazards associated with *Escherichia coli* O157:H7 in raw ground beef. Because Canada's food, drug, and meat inspection laws did not cover this microorganism, the agency developed guidelines for reducing *E. coli* O157:H7 in raw ground beef (Health Canada, 1999b).

- The Animal Plant and Food Risk Analysis Network within the Canadian Food Inspection Agency is responsible for animal and plant health risk assessments.[7]

- The 2000–2002 water-related disease outbreaks that occurred in Walkerton and the Battlefords resulted in governmental inquiries into the causes for these tragic episodes. These major governmental responses led to several reports, some of which recommended the proactive use of microbial risk assessment strategies (Krewski et al., 2004).

- Since 2002, Canada's federal departments, funding agencies, and industry associations have been participating in the Canadian Research Coalition for Safe Food and Water to identify and fund research priorities for public health protection. The first two years resulted in seven interdisciplinary teams focused on gathering environmental and health data to improve outbreak surveillance and risk assessment and management approaches (CIHR, 2006).

2.2.2.3. *Australia and New Zealand*

The microbial risk assessment activities in these two countries have been mainly focused on drinking water. The bases for the Australian Drinking Water Guidelines (NHRMC-NRMMC, 2004) and the National Guidelines for Recycled Water (NRMMC, 2006) are: HACCP principles (Codex, 1997), the Australian/New Zealand Standard on Risk Management (AS/NZS, 1999), and WHO policies (WHO, 2004b; 2001). The 1996 Australian drinking water guidelines were based on state-of-the-art WHO guidance, but officials realized that conducting a comprehensive review of the guidelines in the future would be too time-consuming and costly. As a result, the National Health and Medical Research Council (NHMRC) and the Natural Resource Management Ministerial Council decided to revise the guidelines on a "rolling" basis (NHMRC-NRMMC, 2004). A major change between the 1996 and 2004 versions of the drinking water guidelines is the inclusion of a risk management framework; the 2004 version of the drinking water guidelines also draws on AS/NZS 4360 (1999).

The need for the recycled water guidelines grew out of the recognition that efforts to reduce risks would require assessment of risks, determinations of acceptable or tolerable risk and also health-based targets (NRMMC, 2006). The recycled water guidelines rely on Australia's drinking water guidelines (NHRMC-NRMMC, 2004).

[7] Building on the Animal Plant and Food Risk Analysis Network's methods to address plant and animal health and food safety risks, Ontario's Ministry of Agriculture, Food, and Rural Affairs developed a risk management framework in which risk assessment—involving hazard identification, risk characterization, and biological recommendations—provides the scientific basis for decision-making (Jardine et al., 2003).

2.2.2.4. *France*

MRA has been conducted in response to government officials' requests for analyses and recommendations for supporting decision-making processes. For example, French authorities have asked the French food safety agency (Agence Francaise de Sécurité Sanitaire des Aliments) to make risk management recommendations that incorporate social and institutional views of acceptable risk. The bases for such recommendations have been quantitative risk assessments (Pouillot et al. 2004).

2.2.2.5. *The Netherlands*

MRAs have been conducted to aid decision-making for public health protection improvements. Assessments have included systematic examinations of the health impacts of various sources and routes of exposure and various interventions. The results have assisted decision-makers in determining the most effective and feasible risk management options (Nauta et al., 2005).

2.2.2.6. *Sweden*

In the 1990s, a listeriosis outbreak was associated with widely consumed processed foods (Ericsson et al., 1997). Furthermore, Loncarevic et al. (1996) suggested that salmon and rainbow trout were causes of listeriosis. These results raised public concerns about the safety of traditional foods.

The scientific findings and public concerns led the National Food Administration to characterize related public health risks and identify ways for reducing them. (Lindqvist and Westöö, 2000).

2.2.2.7. *United Kingdom*

Several initiatives in the United Kingdom (UK) have addressed MRA-related issues, and several risk assessment policies are relevant to microbial pathogen risks.

- In the late 1990s, the UK relied on HACCP to address foodborne pathogen risks, but officials recognized that this method might be insufficient for meeting international food trade needs. To advance beyond HACCP, the Ministry of Agriculture, Fisheries and Food funded a collaboration of academic centers (FORA or Food Risk Assessment) to improve risk assessment methods (Medical Research Council Institute for Environment and Health, 2000). The UK developed and published principles for

transparent, consistent risk assessment to ensure the safety of food commodities (Minister of Agriculture, Fisheries and Food [UK], 1998).

- The UK Strategy Unit (2002) includes risk assessment in its risk management paradigm.

- One goal of the Food Standards Agency is to reduce the baseline number of foodborne disease cases by 20% in five years (FSA, 2003 cited in Hill et al. 2003).

- MRA has been conducted to aid the Food Standard Agency's Zoonoses Action Plan in improving the abattoir surveillance program. The results were used to help develop targeted interventions on high-risk farms; thereby reducing the risks of human infection (Coburn et al., 2005).

2.2.2.8. *European Union*

In 1997, the Scientific Committee on Food of the European Commission adopted principles for microbial risk assessments. The committee produced a report, available on the European Union's website.[8] In addition, EFSA's guidance for genetically modified microorganisms and their derived products for use as food or feed describes numerous policy documents that serve as the foundation for the guidance (see p. 59 of EFSA, 2006d).

2.2.2.9. *United Nations*

The United Nations (UN) has numerous policies and activities that are relevant to MRA.

- As early as 1991, the Joint FAO/WHO Conference on Food Standards, Chemicals in Foods, and Food Trade recognized the need for greater consistency and transparency in Codex's risk analyses (FAO/WHO, 1995).

- From 1995, joint FAO/WHO expert groups and consultations have been held to discuss MRA issues and to develop principles and guidelines for MRAs.

- In 1996, the Codex Committee of Food Hygiene recommended that efforts be undertaken to advance and harmonize microbial risk management strategies.

- The Joint FAO/WHO international risk assessment advisory body was convened in 1997. Within two years, Codex declared microbial pathogen risks urgent issues and adopted guidelines for MRA conduct (Codex, 1999).

- WHO prepared a draft international MRA strategy and mechanism (FAO/WHO, 1999).

[8] Http://www.europa.eu.int/comm/food/fs/sc/oldcomm7/out07_en.htm. Accessed on March 4, 2006.

- The Codex Committee of Food Hygiene prioritized 21 pathogen-commodity combinations as public health concerns, and recommended that FAO and WHO evaluate these jointly through expert consultations (WHO, 1999). The agencies established the Joint FAO/WHO Expert Meetings on Microbial Risk Assessment to design and conduct MRAs.

- WHO's initiative to address *Vibrio* spp. risks related to seafood led to the conduct of MRAs by WHO (2005) and FDA/CFSAN (2005).

- WHO's *Guidelines for Drinking Water Quality* served as the basis for the agency's recent MRA of cryptosporidium in drinking water supplies (WHO, 2006a).

2.2.3. Technical Forces

Trends among scientific and technical experts also supported the development of MRA frameworks, methods, and tools. Although microbial risks were recognized as important, the typical risk management strategy focused on control of indicator organisms rather than assessments of risks.

2.2.3.1. *United States*

In the early 1990s, several research teams applied the chemical risk assessment paradigm to microbial pathogen issues, but found the NRC paradigm problematic and limiting in cases where agent or pathogen dynamics needed to be incorporated in the assessment. Modifying a framework proposed by EPA staff, Sobsey et al. (1993) proposed a framework specifically for MRA.

The EPA Office of Water and ILSI convened a workshop of experts to develop a framework for all microbial pathogens in all media (ILSI, 1996). This conceptual framework was developed to organize information for quantitative microbial risk assessment of all forms of microbial pathogens in all types of aqueous media. Two case studies were commissioned to study the value and flexibility of this framework that resulted in a revised model expected to be applicable to a wider range of exposure routes (ILSI, 2000; Soller et al., 1999; Teunis and Havelaar, 1999). This ILSI initiative stimulated other researchers to examine key issues related to MRA, such as social risk factors and susceptible subpopulations (Balbus and Parkin, 2000; ILSI, 2000).

2.2.3.2. *International*

In 2000, the International Workshop on Promotion of Technical Harmonisation on Risk-Based Decision Making was held in Europe to develop generic standards for risk-based decision-making (Jardine et al., 2003). One outcome of this workshop was a list of five decision steps: identification/characterization, analysis, assessment, management, and decision-making. The workshop report also noted that risk decisions are highly context-dependent and require early involvement of stakeholders. Because of these realities, a suggested—not prescriptive—risk assessment framework was recommended. While technical steps were laid out generically and methods and approaches suggested, the exact steps were not detailed.

3. GUIDING PRINCIPLES AND CONCEPTS

Guidelines for MRA often include statements of principles and descriptions of conceptual issues that are considered when assessing the impacts of microbial pathogens. Many peer-reviewed articles and governmental policy documents are available to guide both risk assessors and risk managers for developing MRA processes and procedures both for general purposes as well as specific applications to real-world concerns.

The purposes of this section are to define "principles" and "concepts," present ones that have been linked to MRA, and point out ones emphasized by specific governmental entities.

3.1. PRINCIPLES

In a comprehensive review of risk management frameworks, Jardine et al. (2003) defined "principles" as "a standard, ideal, rule, or code of conduct"; they also noted that agencies use the term "principles" differently. Their definition was used in this project for identifying and organizing the standards and rules for MRA found in peer-reviewed literature and governmental documents.

The majority of MRA guidelines and frameworks include fundamental principles and best practices for guiding the conduct of MRAs (Table 1). The overarching goal of MRA is to identify pathogen scenarios and options for reducing hazards; thereby assisting decision-makers by meeting their informational needs. MRA can be considered as both process and product. It provides a structure for compiling and evaluating scientific information and produces a statement about the probability and extent of harm to exposed populations.

Drawing from a wide range of documents, the most commonly found principles for MRA were

- Make health protection the priority.
- Conduct processes based on sound science, weighing the evidence.
- Ensure transparency, through mechanisms such as open processes and clear documentation.
- Use and document structured, consistent processes.
- Provide flexible guidelines, not rigid requirements.
- Keep risk assessment and risk management functionally separate, while allowing for ongoing, transparent and appropriate opportunities for exchanges of information.

- Ensure clear, concrete and specific questions early in the process.
- Clarify assumptions and uncertainties.
- Permit iterations of the process, allowing new information to be used and the assessment to be updated.
- Provide outputs relevant and useful to decision-makers.

One of the most important principles—transparency—typically refers to two issues: 1) documentation of methods, models, sources of data, assumptions and uncertainties, and 2) open decision-making processes including forums with stakeholder participation, selection of peer reviewers, and means to review and update MRAs when new data and/or conditions may affect related goals or outcomes. Transparency is improved when MRA modeling results are evaluated and clearly presented with information about the impacts of assumptions and sources of uncertainty.

One of the less frequently found principles was that the precautionary principle can guide public health protection strategies. Other less commonly noted principles were that MRAs could

- Begin with a clearly defined statement of purpose
- Rely on a simple conceptual model sufficient to meet decision-makers' needs
- Ensure efficiency, effectiveness, equity, fairness, and accountability
- Not allow available data to dictate the model
- Base models on physiopathology and the natural course of disease
- Use a strategic focus and sustainable approach
- Simulate realistic scenarios
- Use clear methods
- Consider all available scientific evidence
- Use reasonable and consistent assumptions
- Be based on defined principles and procedural steps
- Be evaluated

In microbiology, there is no "zero-risk" option, which refers to the common assumption that only one microorganism can initiate disease. As a result, risk managers tend to take a

conservative public health approach and identify interventions that will provide the level of safety expected by society. Because pathogens are pervasive in the environment, and it is impossible to remove them entirely, the HACCP approach, for example, has typically been adopted as a viable method to minimize risk to populations (WHO, 2006b).

The following sections discuss how various government agencies approach MRA and present the principles that agencies emphasize.

Table 1. Comparison of microbial risk assessment principles

		Principles									
Year	**Source**	Health Protection Priority	Sound Science/ Weight of Evidence	Transparency	Structured, Documented and Consistent	Flexible	Separate Risk Assessment and Risk Management	Problem Formulation	Assumptions, Uncertainties Stated	Iteration	Relevant
1983	NRC				X						
1993	Sobsey				X						
1995	WHO		X								
1996	ACDP			X	X						
1997	ECFS		X	X	X	X		X			X
1997	FAO/ WHO	X	X	X	X		X		X		
1997	P/C	X	X							X	
1998	EPA – Ecology				X						
1998	UK		X	X	X						
2000	FAO/WHO	X	X	X	X				X		
2000	Health Canada	X	X	X						X	
2000	ILSI		X	X		X		X	X	X	
2000	WHO	X	X	X	X	X	X				
2001	FDA		X	X						X	
2002	FAO/ WHO			X	X				X		X
2000	EC			X	X		X		X	X	
2003	FAO/ WHO	X		X	X						
2003	EPA – Yoe		X	X	X	X				X	
2003	OECD/WHO	X	X								
2004	Canada		X							X	
2004	NHMRC-NRMMC	X	X	X	X				X	X	X
2005	IRGC			X	X	X					
2006	NHMRC	X		X	X	X			X	X	X
2006	FAO/ WHO			X	X						

X

3.1.1. United States

3.1.1.1. *Interagency Risk Assessment Consortium*

To help the Interagency Risk Assessment Consortium (IRAC) develop risk assessment guidelines suitable for pathogen risks in water and food, the EPA Office of Water and FDA's CFSAN supported a grant to evaluate USDA, FDA, ILSI, and Codex MRA frameworks and interview experienced microbial risk assessors (Yoe, 2003; IRAC-MRAF, 2002). The important principles that were common among these sources were

- Frameworks be generic but flexible for implementing a variety of pathogen-host-environment scenarios.
- Frameworks should be clear and sufficiently descriptive to facilitate implementation.
- The conceptual model be developed early.
- Assumptions be tracked throughout the MRA.
- Documentation be developed during the MRA to ensure appropriate recall of the assumptions and work conducted.

Based on the interviews, final recommendations to improve MRAs (Yoe, 2003) included

- Adding a formal problem formulation step to the MRA process
- Clarifying the scope of the assessment
- Assuring early development of a conceptual model
- Avoiding constraint of initial risk assessment questions, due to limited data availability
- Developing an explicit list of questions iteratively to guide the MRA
- Designing realistic time lines and resources to support the work
- Defining roles and responsibilities
- Tracking and documenting assumptions throughout the conduct of the MRA

- Assuring unbiased and thorough review processes
- Emphasizing stakeholder involvement
- Stating how researchers can develop needed data and knowledge

The risk assessors interviewed also recommended that the conceptual model be developed early, the assumptions be tracked throughout the MRA, and documentation be developed during the MRA to ensure appropriate recall of the assumptions and work conducted. The results of this initiative indicated the importance of ensuring flexibility in a generic framework, allowing for elements to be used as appropriate for the risk issue and its contexts (Yoe, 2003).

3.1.1.2. *Environmental Protection Agency*

This agency has published many guidance documents to clarify the process and principles to be used in its risk assessments.[9] Its risk characterization guidelines (U.S. EPA, 1995) describe the importance of

- Transparency of the policies and process
- Clarity of the methods and assumptions used
- Reasonableness of the assumptions
- Consistency of the methods and assumptions among risk assessments

These four characteristics were established by agency policy in 1995 (U.S. EPA, 2000a).

3.1.1.3. *Food and Drug Administration*

CFSAN has published guiding principles for risk assessment (U.S. FDA, 2002) that highlight the value of

- Iteration of risk assessments, with more quantification as data allow

[9] See EPA's Risk Assessment Forum website at http://cfpub.epa.gov/ncea/raf/rafguid.cfm Last accessed on February 15, 2007.

- Open exchange of information and ideas among risk assessors and decision-makers
- Focusing risk assessments on meeting decision-makers' needs
- Simplicity of the model, using approaches sufficient to meet decision-makers' needs
- Transparency of the modeling and decision-making processes
- Use of high-quality data, assured through data audits and verifications
- Credibility through the validation of models, analysis of uncertainty, and peer review of risk assessments

To improve the management of MRA processes, realistic time frames and resources, and opportunities for staff to build MRA capabilities have been recommended (U.S. FDA/CFSAN, 2002).

3.1.2. Canada

Canada's fundamental principles for risk management (Health Canada, 2000) include

- Improving health through a "precautionary" approach
- Involving stakeholders in a process tailored to fit the issue in its real-world context
- Communicating effectively
- Using a broad perspective, as well as integrated and collaborative approaches
- Using sound scientific advice
- Making the risk assessment and decision-making processes transparent

3.1.3. Australia and New Zealand

Important principles cited in MRA policy documents for these two nations include

- The goal of MRA is to protect public health.
- MRA can identify significant issues and hazards.

- MRA requires a structured, systematic and transparent process.
- The breadth and depth of the MRA approach should align with the complexity of the problem and the potential risk level.
- MRA outcomes should be evaluated.
- Uncertainties need to be addressed in MRA.
- Risk management decisions should be based on health-related values derived from MRA.
- MRA targets should be verified using monitoring and field audits.
- MRA should involve stakeholders and other agencies in the process.
- Risk communication strategies should involve approaches suitable for the public and agency employees.
- Public trust and confidence must be maintained.

3.1.4. France

The French Food Safety Agency relies on the risk assessment principles put forth by the FAO/WHO (FAO/WHO, 2002a cited in Pouillot et al., 2004).

3.1.5. The Netherlands

MRAs in The Netherlands focus on representing reality as comprehensively as possible. They construct a series of mathematical models aligned in a "farm-to-fork" chain. This is the approach that was used by Nauta et al. (2005).

3.1.6. Sweden

The Swedish food safety agency's MRA principles include: transparency, clearly stated assumptions, and evaluation of uncertainty and variability. Sweden has promoted the use of Monte Carlo methods for effective evaluation of MRA (Lindqvist and Westöö, 2000).

3.1.7. United Kingdom

Principles that guide MRAs in the UK are based on the 1999 guidelines of Codex Alimentarius Commission (see section 3.1.9.1 below and Hill et al., 2003). Additionally, the UK emphasizes:

- Examination of the impacts of parameters on possible control strategies
- Iterative processes
- Identification of data limitations
- The use of HACCP principles

Furthermore, the UK's Advisory Committee on Dangerous Pathogens articulated the importance of ensuring that MRAs are conducted consistently and explicitly, based on science, and open for public and expert scrutiny (ACDP, 1996).

3.1.8. European Union

The Scientific Steering Committee has issued a number of reports to harmonize risk assessment practices, articulating many of the same concepts found in the United States and other nations. Efforts to advance exposure assessment have led to a modular process risk model, which represents six components in the farm-to-fork pathway: growth, inactivation, portioning, mixing, removal, and cross contamination. A model is developed for each of these modules,[10] based on available scientific data. The assumptions, uncertainties, and limitations are noted when the outputs of the exposure assessment are presented to decision-makers. This report also notes the importance of risk assessors effectively communicating their data needs and assessment products to risk managers and other scientists. Recommendations for ensuring effective communications are included in the report (EC, 2000).

3.1.9. United Nations

3.1.9.1. Codex

This organization's seminal statement of principles for microbial risk management was published in 1999, along with guidelines for conducting MRAs (Codex, 1999). The principles emphasize the importance of

[10] The term "module" is used in this report to refer to self-contained units that perform a specific task or function within an overall problem system. Modular approaches to microbial risk assessment have been developing through initiatives of the FAO/WHO committees and food-related agencies of The Netherlands and United States.

- Sound science
- Functional separation of risk management and risk assessment
- Use of the traditional four-compartment model (e.g., NRC, 1983)
- Clarification of the MRA's purpose and constraints
- Transparency of the process
- Description of uncertainties
- Use of good quality data
- Consideration of the dynamics of microbial life cycles
- Reiteration and evaluation of the results, as needed to keep the information current

Codex expanded these principles a few years later (FAO/WHO, 2002b), adding and emphasizing the following concepts.

- Priority of human health protection
- Clear risk manager-stakeholder communication
- Documented processes
- Clear MRA objectives defined in advance
- Role of uncertainty in informed decision-making
- Need for precautionary approaches
- Use of a comprehensive, structured process; e.g., involving the whole food chain (from production to consumption) and identification of available risk management options
- Necessity of feasible and effective risk controls

Codex also defined ten principles to facilitate the conduct of MRAs (Codex 2003). These include

- Clarifying the scope and purpose of the MRA
- Selecting experts in a transparent process
- Conducting MRAs in accordance with defined principles and steps
- Using all available scientific data
- Examining all risk-related components from production to consumption
- Declaring constraints
- Stating assumptions
- Describing uncertainties
- Using realistic exposure scenarios
- Presenting the final results in usable forms

3.1.9.2. *Joint FAO/WHO*

The Joint FAO/WHO Expert Meetings on Microbial Risk Assessment (JEMRA) provide technical support to Codex for its deliberations, conduct risk assessments, and provide information and advice to Codex and its member countries (FAO/WHO, 2003a). By 2000, JEMRA had produced several reports that documented the principles for MRAs and how MRAs should be conducted.[11]

A joint consultation in 2002 revealed important lessons for further development of MRA principles and guidelines (FAO/WHO, 2002a). As in other workshops, the participants noted the importance of transparency, credibility, and the use of good quality data and peer reviews.[12] Participants in this consultation noted the need for

- Risk managers and assessors to communicate throughout the MRA process to ensure that the purpose and scope are clear
- Sufficient resources to start and complete the assessment

[11] See WHO's website at http://www.who.int/foodsafety/publications/en

[12] See Table 1.

- Continuing coordination of contributors
- Useful products

Annex III of the consultation report defines the purpose of an MRA as "the objective interpretation of relevant scientific knowledge to help the risk manager make an informed decision" and describes how to develop an MRA's scope and conduct the MRA process (FAO/WHO, 2002a). The report also points out that existing MRA modules (e.g., for the production-consumption chain of events examined in exposure assessment) could be shared among risk assessors, thereby reducing time and effort in subsequent MRAs.

In 2003, FAO and WHO articulated the following principles specifically for MRA (FAO/WHO, 2002b; 2003a):

- MRA should provide risk managers with a "best estimate" of the risk and dose-response relationship, as free from bias as possible.
- Uncertainty and variability should be tracked throughout the model and included in the final estimate.
- Independence and separation of hazard characterization and risk management are essential.
- Interaction between risk assessors and managers is necessary to ensure that the final product is useful, understandable, and relevant to policy-makers.
- Transparency requires full documentation of the process, including sources of data, an evaluation of the quality of the data, and any assumptions made to implement the MRA.
- When selecting mathematical models, issues to consider include the goodness-of-fit, conservativeness, mechanistic relevance, and flexibility of the model. They noted that modelers should be wary of becoming too attached to any particular model; modelers can achieve objectivity by thoroughly checking the fit of the model to the data.

These agencies also state that the MRA process will vary due to the nature of the pathogen being analyzed and the interdependence of steps and the sequence and timing of events in the process being modeled. Furthermore, modelers carefully define "infection" and the spectrum of adverse outcomes linked to exposure to the pathogen. These definitions ought to be

based on a thorough understanding of the physiopathology of the disease and the "natural history" of the disease (FAO/WHO, 2003a).

An additional principle of "substantial equivalence" was stated in a joint FAO/WHO expert consultation on the safety assessment of foods derived from genetically modified animals (FAO/WHO, 2003b); for example, traditional food products should serve as the baseline for judging safety of newly derived foods.

3.1.9.3. *World Health Organization*

In 2002 WHO issued a set of draft principles and guidelines to conduct any type of microbial risk management process, including risk assessment (FAO/WHO, 2002b). These principles were

- Protection of human health should be the primary consideration in risk management decisions.
- Risk management should include clear, interactive communication between stakeholders during various aspects of the process, as appropriate.
- Processes and decisions should be transparent and fully documented.
- The establishment of risk assessment policy is a responsibility of the risk managers. The objective of risk assessment should be clearly defined before the risk assessment begins.
- The scientific integrity of the risk assessment process should maintain the functional separation of risk management and risk assessment, while ensuring transparent and appropriate interaction between them.
- Risk managers should take into account the uncertainty of the risk estimate when making risk management decisions.
- In the case where scientific knowledge of the risk is insufficient, it may be appropriate for risk managers to apply a precautionary approach, through interim measures.
- To arrive at a decision, risk management should follow a structured process and must include identification of available risk management options and their likely impact on mitigating risk to human health.
- Risk management decisions should take into account the whole food chain from primary production to consumption including imported foods, and should be

implemented in the context of appropriate food safety infrastructures (e.g., regulatory enforcement, food product tracing systems).

- Risk managers should ensure that any control measures that are to be implemented should be feasible, effective, and proportionate to the risks identified.

- Risk management decisions should always be open to review when new information becomes available that substantively alters the conclusions of the risk assessment or its associated degree of uncertainty or as new risk management options become available.

- The effectiveness of risk management measures should be assessed periodically with regard to the risk management goals, and the measures should be revised as appropriate.

- Risk management goals should be periodically assessed in order to encourage continuous improvements relating to public health risk.

3.2. Concepts

The term "concept" usually refers to general ideas or understandings that are derived from and informative for addressing specific instances or occurrences. This report adopts the term "concepts" to compile the key issues noted by assessors and managers of microbial pathogen risks. Some of the overarching concepts most often mentioned in MRA policy documents and peer-reviewed literature include

- Consider the dynamic dimensions of the pathogen, environment, host, and human population.

- Construct a conceptual model early in the process.

- Model realistic conditions.

- Use a comprehensive source-to-exposure pathway paradigm to organize information and construct a series of linked mathematical models.

- Recognize the interrelated nature of steps in the paradigm, such as the sequence and timing of events.

- Clearly define terms including "infection" and health outcomes.

- Clearly define the outcome metrics (individual and/or population scale), and ensure that they link to the decision-makers' needs.

Two dominant types of MRA are risk-ranking exercises and product pathogen pathway analyses. Risk ranking has been used to prioritize multiple risks and determine resource allocations (U.S. FDA/CFSAN, 2002). Pathway analyses assess the entire pathogen transmission process from environmental source to human exposure. This organizational tool helps risk assessors and modelers identify the many elements to consider for the model, recognize the types and sources of data needed for modeling and the relative importance of elements to consider when constructing the mathematical models. For instance, the comprehensive framework used in FDA's risk assessment of raw oysters (2005) demonstrates that a rich mix of data sources can be combined to implement an effective MRA. Pathway modeling results are used to estimate the risk of adverse outcomes within a population. MRAs of pathogens in recreational water (Soller et al., 2003), biosolids (Eisenberg et al., 2004), and processed foods (USDA, 2005b) have included more comprehensive pathway modeling than is typically seen in chemical risk assessments.

Many issues in MRA differ importantly from chemical risk assessment, demanding different conceptual and practical modeling approaches (WHO, 2005; Schaub, 2004; FAO/WHO, 2003a; OECD/WHO, 2003; Eisenberg et al., 2002; Parkin, 2002; Medical Research Council Institute for Environment and Health, 2000; ILSI, 2000; Haas et al., 1999; ECFS, 1997). The unique characteristics of microorganisms and host populations and their dynamic aspects ought to be considered carefully when designing an MRA approach (Buchanan, 2003). Specific concepts that should be addressed in MRAs are highlighted in the following sections; these are listed according to their likely placement in a source-to-response model.

3.2.1. Pathogen Characteristics

In the absence of seasonality or other data, modelers assume that microbes are spread evenly in the environment, although heterogeneous distribution is likely. Similarly, there are limited data to indicate the number of organisms necessary to cause adverse health effects. Due to variations in strain, life stage, and survivability, not all individual pathogens in the environment are capable of inducing illness; however, for modeling purposes they are all assumed to be viable and pathogenic. Following is a summary of pathogen characteristics that may contribute to the MRA modeling process:

- Microorganisms can self-replicate. Even if one cell is not sufficient in and of itself to induce pathogenicity in humans, one microorganism may have the capacity to grow within the body and develop a colony that is sufficient to induce a pathogenic process (Haas et al., 1999).

- Strains vary in virulence. For example, the variations in infectivity of strains of *Cryptosporidium parvum* have been identified based on human challenge trials (Chappell et al., 1999), but the significance of these variations at the human population scale has not yet been determined. Such variations may affect dose-response relationships (Coleman et al., 2004).

- Pathogens may evolve in terms of their virulence and other key characteristics, (e.g., as they pass through various infected individuals and other hosts). Some pathogens may lose their virulence as they pass from the initial human (animal) host to a second and/or third host, accounting in part for the decline in disease outbreaks.

- Microorganisms can grow as conditions change during the movement of food from the farm to the table. The pH, water content, temperature, and salinity of food matrixes are known to be important, influential characteristics of foods that affect pathogen dynamics (e.g., USDA, 2005a).

- Characteristics of the microorganism, such as viability and resistance, may also affect the dynamics of disease outbreaks. For example, the chemical and/or thermal processes used in food processing and/or water treatment systems reduce the viability and survival of many microorganisms before foods, food products, and drinking water reach consumers. Furthermore, if microorganisms are not viable and infective when susceptible hosts come in contact with them, they will not cause infection in those hosts.

- Pathogens vary in detectability, and sampling recovery rates. Sampling collection and laboratory detection procedures may not preserve 100% of the actual concentration levels of the pathogen in environmental media (air, water, foods, etc.). The degree of loss between the environment and the laboratory detection level varies, and ought to be considered in MRA modeling whenever possible.

3.2.2. Environmental/Media Conditions

When developing the pathway component of conceptual models, assessors thoroughly consider the ways in which a pathogen moves from its source(s) to humans. Pathogens are found in air, drinking water, recreational water, wastewater, biosolids/manure, soil, fresh and processed foods, products such as industrial and pesticidal formulations, etc. In each of these media, pathogens encounter environments that are more or less favorable to their growth, transport, survivability, viability, and pathogenicity. Mechanisms of release from sources, intermediate hosts or reservoirs, life stages and forms, and the impacts of human interventions (such as chlorination and filtration of drinking water supplies) should be considered. Environmental conditions frequently change the number, concentration, and form of pathogens in human exposures. For example,

- Pathogens are not usually suspended evenly in water or other media. Food and soil-related matrices tend to have more specific, localized boundaries (e.g., egg shells, packaged, food products, biosolids) and binding properties that permit focused microbial growth and more readily identifiable contamination than do media without such binding properties or specific boundaries (e.g., ambient air, flowing bodies of water).

- Environmental conditions may permit long-term survival of the microorganism. Because of specific life cycle and other characteristics, some pathogens (such as anthrax) can infect humans decades after the pathogens have appeared in the ambient environment.

- Other species may serve as intermediate hosts providing additional pathways for the microorganism to spread. For some pathogens, animal and insect vectors may be important steps in the disease transmission process (Haas et al., 1999), which may need to be considered in MRA models.

- Intervention strategies such as chlorination and irradiation may affect the viability of the pathogen. Worldwide chlorination has been successfully used to inactivate microbial pathogens in drinking water (Embrey et al., 2002).

3.2.3. Host Characteristics

For MRAs, characteristics of hosts need to be considered on individual and population scales. Age, gender, prior disease and exposure, and medication status, immune status, socioeconomic status, and other factors may all be needed to implement MRAs. Although many of these variables can be considered in a conceptual model, they usually cannot be modeled mathematically due to the lack of appropriate data; however, some MRAs (e.g., U.S. EPA, 2005b; Makri et al., 2004) have been able to account for at least several of these aspects of human response. Information on specific host characteristics to consider in microbial risk assessment include the following.

- Susceptibility to infection and disease depends not just on individuals' health status, but also their pre-existing immunity and pathogen exposures.[13] Individual susceptibility depends on many factors, some that are host-specific and some that are not. Determinants of susceptibility include age, pre-existing chronic disease, and simultaneous pathogen exposures (Haas et al., 1999).

[13] Population variations in genetic makeup and immune-susceptible proportions are important. For example, strains of *Campylobacter jejuni* and related population immunity and illness rates vary around the world (Parkin and Hawkshead, 2003).

- Human populations are not homogeneous in their genetic makeup or immune and asymptomatic carrier status. The proportion of immune and susceptible individuals in a population varies; for example, strains of *Campylobacter jejuni* and related population immunity and illness rates vary in different parts of the world (Parkin and Hawkshead, 2003).

- Subpopulations which may be of concern include the young, the elderly (especially those with underlying diseases), the malnourished, and persons with HIV/AIDS or other immunocompromised conditions, lupus, cystic fibrosis, and transplant and chemotherapy patients (Rose, 1997).

- A pathogen's persistence in an individual and the individual's shedding of the pathogen leads to continued risk of secondary and tertiary spread. The longer a pathogen is viable and shed in infective form by hosts, the longer that the microorganism has the capacity to initiate pathogenic processes in additional hosts.

- Population characteristics, such as immunity and social behavior, are potentially important. Social factors that may affect immunity include access to health care; for example, the lack of access increases the probability of chronic disease conditions being under-treated, thereby reducing the individual's capacity to mount an effective immunological defense (Balbus and Parkin, 2000).

- Intervention strategies such as vaccination and pasteurization may affect the disease process on individual and population scales. Public health interventions have historically contributed to declines in the occurrence of infectious disease, and may serve as the bases for developing risk management options for selected pathogens with effective interventions (e.g., HACCP controls for foodborne pathogens such as salmonella).

3.2.4. Exposure

The number and/or concentration of pathogens per unit volume are needed for exposure assessment. Estimating the number of pathogens that may come into contact with humans are very challenging and require considerable modeling skill.

Depending on the medium in which the pathogen is found, rates of inhalation, ingestion, and/or dermal contact may be needed for risk calculations. Although detailed consumption data sometimes exist, the data often do not describe foods or consumption patterns in sufficient detail, include information on sensitive subpopulations, or provide sufficient details about food processes. As a result, risk assessors have had to rely on aggregated, insufficiently detailed, or inaccurately targeted data (Barraj and Petersen, 2004). Most modelers use a point estimate or population average (e.g., two liters of water/person/day) (U.S. EPA, 2000b).

Other exposure factors to consider include

- Single exposures are sufficient to present risk. To implement a conservative public health approach in MRAs, modelers often assume that only one, single, exposure to a microorganism is sufficient to induce a pathogenic process in human hosts (Haas et al., 1999). Although this concept may conflict with evidence for some pathogens (e.g., where family members are the predominant hosts or secondary hosts in an outbreak), the single-exposure assumption aligns with the no-threshold, dose-response approach typically used in MRAs.

- Each exposure is an independent, non-cumulative event. For the purposes of MRA modeling, current statistical methods require that each exposure be treated as an independent event (Haas et al., 1999). Although each exposure may not be independent in an outbreak (e.g., where family members are exposed to the same case over days or weeks), current statistical methods cannot account for the interdependence of related exposures.

- Exposure to pathogens may lead to immunity. Humans can develop immunity to many pathogens from one or more exposures, but the determining factors of immunity are unclear. Dynamic disease models either include the known proportion of the population that is immune, based on clinical and/or field evidence, or assume that a proportion of the host population can become immune to a pathogen (ideally based on evidence for a similar pathogen) (e.g., Eisenberg et al., 1996).

3.2.5. Dose

Estimating whether a microbial pathogen can overcome physiological barriers and reach the target tissue is not always easy. MRA typically deals with a single cell or unit of infection. In many cases, modelers have assumed a non-threshold approach—that one pathogen reaching the target tissue is sufficient to initiate the disease process (Haas et al., 1999).

Researchers have used many data sets to develop dose-response curves for a variety of microorganisms. These efforts have produced about ten different mathematical forms to consider for MRAs (Haas et al., 1999). For many microbial pathogens, two-parameter models, such as the commonly used beta-Poisson model, have been found to perform at least as well and sometimes better than more complex models (Moon et al., 2004).

3.2.6. Human Health Responses

Additional issues in MRA modeling arise from the need to recognize that a pathogen may be capable of inducing a range of human health responses both in individuals (e.g., asymptomatic infection, acute illness, sequelae, death) and populations (e.g., incident case rates, hospitalization rates, mortality rates). On the population scale, the rate of disease spread varies depending on numerous factors, such as

- The proximity of infected and susceptible populations
- The viability and concentration of the pathogen in the material excreted by one host and transmitted to another (secondary spread)
- The virulence of the strain

On the individual scale, there may be a wide range of clinical outcomes linked to a specific pathogen (Asano et al., 2007), and the range of severity of outcomes linked to a specific pathogen can be considerable (Haas et al., 1999). For example, in individuals, *C. jejuni* is known to cause Guillain-Barré Syndrome in a small portion of the population, along with more common, acute episodes of diarrhea (WHO, 2002b). Some Guillain-Barré cases resolve in three weeks with no paralysis, while others result in long-term, significant paralysis (WHO, 2002b). Data on pathogen and disease dynamics and the impacts on susceptible subpopulations can be effectively modeled for some pathogens (Eisenberg et al., 2004). Furthermore, social and economic impacts secondary to health impacts can be modeled as proxies when direct health data are not available. For example, data on the use of over-the-counter medications, visits to hospital emergency departments, and days of lost work or school time may be used to estimate the impacts on human health.

3.2.7 Modeling

Converting a conceptual model or pathway model into a series of mathematical models requires attention to technical and data quality concerns. Following is a summary of modeling issues to consider in microbial risk assessment:

- It is recommended that mathematical models be flexible and represent the level of conservatism set by risk managers, and effectively model parameter relationships as judged by goodness-of-fit evaluations.
- Static models for MRA have been in use for several decades (Haas, 1983), but are not the most useful for all pathogens (Asano et al., 2007).
- Where infectivity or pathogen life cycle dynamics are important determinants of disease in human populations, infectious disease models may be more appropriate (e.g., Eisenberg et al., 1996). However, such dynamic models usually require more

extensive data, and potentially more computing power, which limits their feasibility (Asano et al., 2007).

- Dynamic aspects of agent and host populations—including population changes in susceptibility and behaviors—can be considered. Both microbial pathogens and human hosts are living entities that change in many ways during their life cycles. The changes that occur in each may affect the probability of human disease in both direct and indirect ways (Haas et al., 1999).

- Modeling processes may be highly complex, and may be incomplete or infeasible due to the lack of data. Conceptual models covering pathogen sources to human illness usually involve many steps (e.g., U.S. FDA/CFSAN and USDA/FSIS and CDC, 2003). The availability of data to characterize all of the components and processes in such a model is quite variable, which leads to cumulative, extensive uncertainties in the final results.

- Few MRA models have been validated because of the lack of data to test models for different locales and/or conditions.

- Data gaps limit the precision of MRAs. Uncertainty in modeling is often related to the lack of relevant empirical data to quantify the concentration of pathogens in the environment and in exposures; to accurately determine the shape of the dose-response relationship curve; and to measure the magnitude of epidemic (as distinct from endemic) adverse health effects (Haas, 2002; Haas et al., 1999).

- The impacts of uncertainty and variability need to be assessed on MRA results and communicated to risk managers.

A summary of key issues in modeling microbial pathogen risks are shown in Table 2.

Table 2. Key Issues in Modeling Microbial Pathogen Risks

Microbial Pathogen	• Taxonomy • Strain • Ecology • Survival • Characteristics that affect growth • Life stage • Viability • Infectivity and incubation period
Environment	• Medium (e.g., food, water, soil, air) • Characteristics of the medium (e.g., acidity, presence of other microorganisms) • Temperature • Time, season
Human Host	• Age • Gender • Nutritional status • Immune status • Pre-existing disease • Susceptibility to the specific microbial pathogen • Range of health outcomes • Severity of outcomes • Proximity and behaviors of infected and susceptible populations
Relationships between the Pathogen, Host and Environment	• Virulence of the microbe • Host specificity • Environmental conditions that contribute to exposure • Mechanisms of infection • Secondary spread
Modeling	• Adequacy of conceptual framework • Ability to characterize all aspects of the framework • Static vs. dynamic models • Characterization of the dose-response relationship
Sources of Uncertainty and Variability	• Data quality • Measurement • Assumptions
Model Validation	• Availability of data

3.2.8. Sources of Data

Accessing appropriate data for MRAs involves many issues. Sources may include research and clinical data, epidemiological and human exposure data, as well as environmental or food monitoring data. Examples of issues to consider follow:

- Not all sources of data are readily accessible—particularly human health data that may require institutional review board clearance to protect human research subjects. Other types of data may not be in the public domain or available to persons outside of the organization that collected the data.

- Many data sources have limitations in scope, timeliness, and relevance to the pathogen and/or population of concern.

- Sources may not be accurate or precise. For example, pathogen recovery rates and the proportion of infective microorganisms detected in an environmental sample are typically fraught with sampling and analytic limitations. Sampling pathogens in drinking water is known to have significant field limitations; furthermore, distinguishing the infective strains of pathogens is often impossible.

Disease outbreak data may provide insights about the potential for secondary and tertiary disease transmission, the magnitude and severity of infection and illness, and other characteristics of disease dynamics. While some modelers assume that outbreak or surveillance data are sufficient to use in MRAs to assess microbial-related health effects (e.g., Soller et al., 1999), others have noted important limitations of surveillance and outbreak data and have questioned the value of these data for modeling microbial pathogen risks (Makri et al., 2004; Flint et al., 2005). In the absence of better data, however, surveillance and outbreak data—with all of their potential flaws—may be the best data sources available. When necessary, outbreak data is used with explicit recognition of their limitations. In some instances, it may be possible to adjust reported surveillance or outbreak data and estimate the number of all actual cases (i.e., both the reported and non-reported cases) (Flint et al., 2005).

4. MICROBIAL RISK ASSESSMENT FRAMEWORKS

Currently, four fundamental types of microbial risk assessment frameworks exist. One type uses the chemical risk assessment framework described in section 2.1.1 (NRC, 1983); another type uses a modified NRC framework, in which the two middle steps are sometimes reversed; a third framework builds on the NRC approach by adding a problem definition step (e.g., part of planning and scoping, or problem formulation) (U.S. EPA, 2005a, 2004b, 1989); the final type of framework was developed by ILSI (2000).

Table 3. Categories of microbial risk assessment frameworks with MRA examples

1. NRC, 1983	
• WHO, 1995	• Pouillot et al., 2004
• Haas et al., 1999	• U.S. EPA, 2004a
• Lindqvist and Westöö, 2000	• Coburn et al., 2005
• Hill et al., 2003	• EFSA, 2006a, 2006b, 2006c and 2006d
• EFSA, 2006a	• U.S. EPA, 2006b
• NZFSA, 2004	
2. Modified NRC, 1983 without an explicit problem definition step	
• Sobsey et al., 1993	• USDA, 2001
• ACDP, 1996	• FAO/WHO, 2003b
• Medical Research Council Institute for Environment and Health, 2000	
3. Modified NRC, 1983 with problem definition	
• ECFS, 1997	• OECD/WHO, 2003
• Codex, 1999	• NHMRC-NRMMC, 2004
• WHO, 1999, 2004b, 2005 and 2006a	• Nauta et al., 2005
• U.S. FDA, 2001 and U.S. FDA/CFSAN, 2005	• USDA, 2005a and 2005b
4. ILSI, 2000	

The approach that Sobsey and colleagues (1993) proposed is an example of a modified NRC framework that is a risk-based conceptual framework for microbial risk assessment based on a model presented in an EPA research strategy report (cited in Sobsey et al., 1993). The flow-diagram model began with "microbial hazard identification" and moved into two parallel components titled "exposure assessment" and "effects assessment." These components combined into "risk assessment and characterization," which in turn led to "risk management," which involved microbial indicators and HACCP concepts. Data from microbial assays, human populations, organism-host interactions, and relative risks also contributed to the framework. The authors stated that their approach was designed to systematically identify, analyze, quantify, and characterize microbial risks; compare them to chemical risks; and develop and implement a risk

management plan. Furthermore, they claimed that their model would help scientists and decision-makers identify key issues, information gaps, and research needs.

The following sections describe the frameworks that different organizations are using around the world to conduct microbial risk assessments.

4.1. UNITED STATES

4.1.1. Department of Agriculture

To date, the U.S. Department of Agriculture (USDA) has completed a limited number of MRAs; however, no policy document was found describing the agency's risk assessment methods. The Risk Assessment Division of the Office of Public Health and Science has described its process steps as: developing the conceptual model,[14] collecting and analyzing data, identifying data gaps, modeling the pathogen-related risk, and analyzing uncertainty and variability (USDA, 2005a).

Four MRAs posted on the agency's website were reviewed to assess the agency's approach: three for salmonella, and one for *E. coli*. Two were conducted in closer alignment with the NRC (1983) approach than the other two, but all MRAs revealed very thorough strategies for assessing exposures.

Although researchers conducted earlier quantitative MRAs, the USDA's Food Safety and Inspection Service (FSIS) was the first U.S. regulatory agency to publish a formal quantitative microbial risk assessment (on *Salmonella enteriditis* in eggs and egg products) (USDA, 1998). Two years earlier, other units within the USDA and other government agencies, including the FDA, had begun to provide input for this risk assessment. The product pathogen pathway analysis—from farm to fork—did not explicitly follow the traditional risk assessment paradigm, but it did present a comprehensive evaluation of the many steps in moving food products from the field to the consumer. The exposure assessment included five modules and sixteen pathways in conceptual and mathematical models. The modules were

- Egg production

[14] A conceptual model is a written or visual representation of predicted relationships between pathogens and exposed populations. It may be based on working hypotheses, supported by preliminary data and information, and used to organize the conduct of a MRA. The model depicts the purpose, scope, and scale of the MRA; identifies variables and data needed to conduct the MRA; and serves as a preliminary or exploratory risk assessment (U.S. EPA, 2005a).

- Shell egg processing and distribution
- Egg products and distribution
- Preparation and consumption
- Public health outcomes

As in most risk assessments, the MRA process helped FSIS identify important data gaps and research needs to improve the risk estimates. The MRA also gave risk managers a way to evaluate mitigation and strategic options for controlling salmonella in eggs and egg products.[15]

In its more recent salmonella MRAs, USDA extensively described two sets of modules for shell eggs and egg products (USDA, 2005b). Table 4 shows the modules used in these paradigms.

Table 4. USDA salmonella MRA modules for shell eggs and egg products

Shell Eggs	Egg Products
• Farm	• Breaking
• Storage 1	
• Pasteurization	• Pasteurization
• Storage 2	• Storage and Preparation
• Preparation	
• Cooking	• Cooking

USDA has also conducted an MRA to examine the impact of lethality standards on salmonellosis from ready-to-eat meat and poultry products (USDA, 2005a). The risk assessment stages (or modules) that the exposure assessment section of the paper identifies and describes are

- Raw material pathogen burden
- Lethality impact[16]
- Compliance-level impact

[15] See also WHO, 2002a.

[16] Note that "impact" refers to the change in pathogen concentration in the raw materials, processed or prepared foods, or food products as they move through the farm-to-fork process. Changes in concentration may occur due to the effects of heating and cooling, storage, pasteurization, cross-contamination, etc.

- Thermal process safety factor impact
- Storage and growth impact
- Reheating impact
- Risk of illness

FSIS asked the National Academy of Sciences to review its risk assessment of *E. coli* in ground beef (USDA, 2001). In this case, the agency more clearly organized the MRA in alignment with the NRC's risk assessment components: hazard identification, exposure assessment, hazard characterization (dose-response), and risk characterization (NRC, 1983). However, the FSIS expanded the exposure assessment component with three farm-to-fork modules: 1) production, 2) slaughter, and 3) preparation.

Although the Academy reviewers praised FSIS for its thorough and comprehensive MRA, the committee's final report noted the impacts of limited data and the use of assumptions, such as the "typical individual." The Academy recommended that USDA provide clearer documentation of its assumptions and detailed methods to enhance the MRA's transparency (NRC, 2002).

4.1.2. Food and Drug Administration

FDA defines risk assessment as both a process and a product and describes several forms of risk assessment models. It uses its assessments to rank risks, analyze product pathways, evaluate risk-risk tradeoffs, and assess geographically bounded risks (U.S. FDA/CFSAN, 2002). The agency's MRA components and concepts are basically the same as those used by USDA, but FDA gives different names to its concepts and conducts its steps in a different order. Nonetheless, FDA tends to use modifications of the chemical risk assessment framework for food-related MRAs.

4.1.2.1. *Center for Food Safety and Applied Nutrition*

Center for Food Safety and Applied Nutrition (CSFAN) researchers described the purposes of MRA as determining what can go wrong, how it can happen, and what the consequences would be (Dennis et al., 2001–2002). Their "generally accepted framework" has five steps: statement of the problem, hazard identification, exposure assessment, dose-response (or hazard characterization), and risk characterization.

A report of the CFSAN Risk Analysis Working Group described the risk assessment as including: hazard identification, exposure assessment, dose-response assessment (or hazard characterization), and risk characterization (U.S. FDA/CFSAN, 2002). The report also briefly described four goals for risk assessment:

- Risk ranking (comparison of risks among several hazards or foods)
- Product pathway analyses (assessment of factors that influence the risk from farm to consumption)
- Risk-risk (evaluation of risk tradeoffs)
- Geographical (focused on factors that limit or foster the scope of a risk occurrence)

Later in the report, the group described four programmatic steps for initiating risk assessments:

- Concept generation (a list of potential MRAs, including their purpose, scope, importance, needs, and potential use)
- Problem identification (classification of the proposed MRA according to whether it should or should not be conducted or whether additional information is needed to determine the classification)
- Data feasibility determination (evaluation and recommendation as to whether qualitative or quantitative risk assessment, risk management, or research would be appropriate)
- Disposition (selection of MRAs to be conducted in the coming year based on technical merit, data feasibility, resource availability, and other factors)

The report also presented the means to conduct risk assessment processes (e.g., assemble the risk assessment team).

CFSAN's extensive risk assessment of *Listeria monocytogenes* in ready-to-eat foods used the four components of hazard identification, exposure assessment, hazard characterization (or dose-response) and risk characterization (U.S. FDA/CFSAN and USDA/FSIS and CDC, 2003), although earlier versions reversed the middle two steps (U.S. FDA/CFSAN and UDSA/FSIS and CDC, 2003; U.S. FDA/CFSAN and USDA FSIS and CDC, 2001). The primary components of

the 2003 assessment (which focused on deli meats) were the exposure assessment and dose-response steps.[17] Two important advances in this MRA were the use of a dynamic Monte Carlo model to estimate levels of contamination as the product moved through the food processing system, and a comprehensive exposure pathway for deli meats that was linked to a dose-response model. The exposure assessment step included assessed contaminant levels from retail to the table and involved distinct mathematical models for estimating

- *L. monocytogenes* levels in retail foods
- Growth between retail and consumption
- Impacts of the interaction between storage times and temperature
- Impacts of thermal inactivation (for selected foods)

This innovative MRA organized food products into categories to put them in rank order (e.g., seafood included smoked seafood, raw seafood, preserved fish, and cooked ready-to-eat crustaceans). Models were then used to estimate levels of individual and public health risks for each category, such as the number of cases of listeriosis per year and the predicted relative risk rankings for listeriosis in three subpopulations (perinatal, elderly, and intermediate age).

In the FDA's MRA for *Vibrio parahaemolyticus* in raw oysters, the agency used a U.S. step[18] to list the risk management objectives, define the geographic and seasonal dimensions of the MRA, and identify data sources before implementing the traditional NRC risk assessment steps (U.S. FDA/CFSAN, 2005). The modules used to assess the conditions and dynamics from the point of harvest to consumption were

- Harvest
- Post harvest

[17] FDA and Exponent, Inc. developed FARE Microbial™ software for conducting probabilistic microbial risk assessment (Exponent, Inc., 2002). The two modules included in the package are for Contamination and Growth, and Exposure. The first tracks contamination levels through a 20-stage farm-to-fork process and generates distributions of contamination at the time of food consumption. The second module produces distributions of pathogen exposure, as Colony Forming Units per food unit, based on demographic and national survey data on food consumption. The output of this module can be used as the input for FDA's dose-response model.

[18] This "scoping" step included many of the elements of EPA's "problem formulation" step (U.S. EPA, 2004b; U.S. EPA, 2005a).

- Consumption

The 2001 draft of this MRA used the sequence of hazard identification, exposure assessment, hazard characterization, and risk characterization (U.S. FDA/CFSAN, 2001). The assessment separately modeled six oyster harvesting regions and four seasons of harvesting. In this earlier version of the exposure assessment step, three modules were used to organize the complexity: harvest, post harvest, and public health.

CFSAN has also used MRA to address food-related bioterrorism concerns. In this case, the modeling components were: hazard identification, hazard characterization, exposure assessment, and risk characterization (U.S. FDA, 2003).

FDA has defined risk communication as the open exchange of information and ideas, and the agency has identified risk communication as a part of the risk analysis process with a status equal to that of risk assessment (U.S. FDA/CFSAN, 2002). Although FDA has little mention of risk communication in its risk assessments, the agency does prepare and web-post interpretative summaries of its MRAs for general public use and technical reports for more detailed-oriented readers (U.S. FDA/CFSAN, 2005).

4.1.2.2. *Center for Veterinary Medicine*

This FDA unit conducted a risk assessment of fluoroquinolone-resistant campylobacter in chickens (U.S. FDA, 2001). This MRA is not a full risk assessment (in the traditional NRC framework) and does not model the "farm-to-fork" pathway typical of most FDA risk assessments. Instead, this MRA uses a quantitative model to link the prevalence of resistant campylobacter in chicken with the prevalence of resistant infections in the U.S. human population due to the chicken consumption. The model outcomes are presented as the percentage of infections among the U.S. population and three subpopulations. The model depends on observational data and requires fewer assumptions than a fully implemented MRA, but it meets the Center's purpose: to assess the impacts of various risk management options. Transparency, consistency of results, and flexibility for examining a variety of conditions were important considerations when the Center for Veterinary Medicine developed this approach.

4.1.3. Environmental Protection Agency

EPA addresses microbial hazards in drinking water and other environmental contexts, such as cleanup sites, wastewater, biopesticides, biosolids/manure, and recreational water.

4.1.3.1. *Office of Pesticide Programs*

Under section 408(p) of the Federal Food, Drug and Cosmetics Act, as amended in 1996 (U.S. FDA, 1996), EPA is required to screen pesticides and other active ingredients for their potential impacts on human health. The Office of Pesticide Programs conducts risk assessments of modified organisms intended for pesticidal use. The assessments follow the 1983 NRC risk assessment framework and vary in detail according to the scientific information available.

4.1.3.2. *Office of Water*

In the past decade, EPA has begun efforts to transfer FDA's and others' experience with foodborne pathogens to the drinking water experience. In the mid-1990s, EPA's Office of Water and the International Life Sciences Institute (ILSI) convened a workshop of experts to design a conceptual framework for assessing risks associated with waterborne microbial pathogens. Building on chemical and ecological risk assessment methods and lessons learned, the workshop participants designed a four-component process that was organized into three steps: (1) problem formulation, (2) problem analysis (with two sub-steps for exposure and human health effects), and (3) risk characterization (ILSI, 1996).

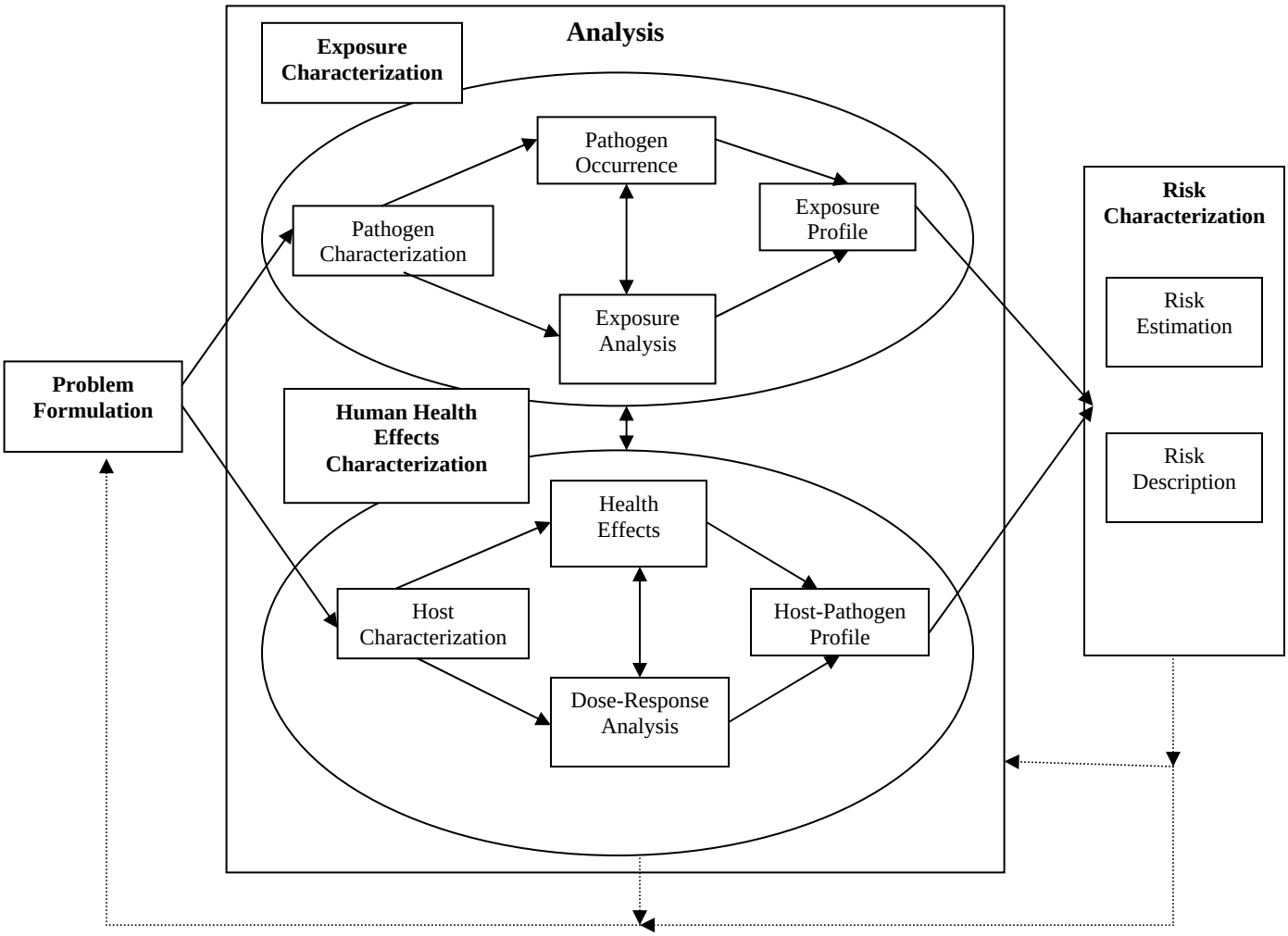
The first step (problem formulation) states the fundamental questions to be addressed, defines the scope and scale of the assessment, and identifies the necessary variables and data. Risk assessors, managers, and stakeholders consider these issues collaboratively to ensure that the end users' needs will be met. The second step (analysis) characterizes the independent and related variations in the organism, host, and environment; discusses the impacts of the variations; and decides the nature of the dose-response relationship. For example, subpopulations are identified, specific pathogen-host relationships are considered, exposure pathways are determined, the impacts of dose variability are evaluated, and uncertainties in the field and laboratory data are examined. The final step (risk characterization) integrates the exposure and health findings; reviews the biological plausibility of the estimated effects; conducts the sensitivity analyses; documents uncertainties and assumptions; analyzes management options (including the use of surrogates and indicators in monitoring programs); and considers the use of measures of effectiveness (such as disability adjusted life years [DALYs]) (ILSI, 2000).

This model has been tested in two case studies, one for cryptosporidium (Teunis and Havelaar, 1999) and one for rotavirus (Soller et al., 1999). The case studies identified modeling issues, information limitations, and data needs, and were used to review and revise the initial

pathogen risk assessment paradigm. The results led to a reorganization of some elements of the model and enhancements and clarifications of several other elements (ILSI, 2000) (Figure 3).

Figure 3. Components of a microbial risk assessment.

Source: Adapted from ILSI, 2000



The ILSI paradigm is similar to chemical and ecological risk assessment approaches (U.S. EPA, 1998; NRC, 1983) with adaptations to account for the unique characteristics of living, microbial hazards and the dynamics that occur in the environment and human populations in the presence of these pathogens. The ILSI paradigm explicitly addresses these unique issues (e.g., pathogens' capacity to grow and remain viable in a variety of environmental media, agent-host specificity, and secondary or person-to-person spread of disease). Another issue is that specific strains of microbial pathogens typically behave differently in humans than in animals. Unlike chemical risk assessment, MRA cannot rely heavily on animal data.

The ILSI framework is sound, but a great deal of research is needed for many microorganisms to fill data gaps and reduce MRA uncertainty, such as the biological mechanisms that cause progression from infection to disease. In addition, data are needed to clarify the distribution of pathogens, the probability of infection following ingestion of organisms at a specific dose, the nature of dose-response relationships, the determinants of illness following infection, as well as the impact of factors such as immune status, prior exposures, and medical conditions (ILSI, 2000).

The ILSI documentation (2000) also notes that risk communication is an important aspect of MRA, and calls for the development of this component in MRAs.[19]

EPA's guidance on risk characterization (U.S. EPA, 1995) indicates that the standard four-compartment risk assessment framework (NRC, 1983) be used. In 2005, the Office of Drinking Water conducted an economic analysis for the LT2 Final Rule and based it on a risk assessment of cryptosporidium in surface and finished water (See section 5.2 in U.S. EPA, 2005b). This risk assessment was conducted in alignment with EPA's risk assessment principles and policies; its purpose was to estimate the pre-LT2 (baseline) annual incidence of pathogen-related illness and death and to compare the estimates to those that would result from implementing different treatment options. The pathogen and related public health concerns were described with attention to subpopulation issues and the quality of available human health data (see section 2.4 in U.S. EPA, 2005b). Following a hazard identification step, the dose-response step included three subcomponents: infectivity dose-response, the risk of illness given infection, and the risk of mortality given illness. The exposure assessment step relied on both individual and population scale data to estimate human exposures to infectious oocysts. The final step, risk characterization, used Monte Carlo methods to combine the results of the dose-response and

[19] Note that in EPA's recent genomics guidelines, the need for partnerships and translating technical information for general audiences was noted (U.S. EPA, 2006a).

exposure assessments for estimating the annual individual and population-scale risks of illness and death. The population scale estimates were made including estimates of secondary spread of disease.[20] The impacts of uncertainty and variability throughout the MRA were analyzed extensively. While considerable attention was given to sensitive subpopulations, data were not available and/or sufficient for estimating their risks.

4.1.3.3. *National Center for Environmental Assessment*

In 1996, the amended Safe Drinking Water Act (SDWA) required EPA to publish a list of contaminants, which became known as the Contaminant Candidate List. In the 1998 and 2005 versions of the list, several cyanobacteria were listed; the later list was based in part on the results of a 2001 EPA-hosted meeting of experts, who identified algal toxins as potential human health concerns. The National Center for Environmental Assessment has produced a series of publications to support the Office of Water's decision-making about such toxins. EPA risk assessment guidelines and the NRC (1983) framework has been used as the structural basis for these publications. The focus of these documents, however, has been on compiling and integrating information for the hazard identification and dose-response assessment steps.

4.1.3.4. *National Homeland Security Research Center*

Risk assessment models are important tools for predicting and prioritizing hazards that may be caused intentionally. Center staff members have described the value of a microbial risk assessment framework for biological contamination incidents (Nichols et al., 2006). Both strategic and tactical applications of MRA are envisioned and described across a planning-preparing-responding spectrum of activities. Prior to an incident, MRA can be used to identify and characterize pathogens, assess potential exposures, prioritize hazards based on probabilities and consequences, and develop threat scenarios and mitigation options. During an incident, specific information can help characterize the exposure and population characteristics resulting in more precise estimates of microbial risks. Following an incident, additional site information can help refine the MRA results, identify appropriate levels for decontamination of affected sites, and assess related hazards.

The Center's preliminary MRA framework for bioagent incidence response is based on a compendium of MRA studies and methods published between 1994 and 2004. The framework is comprised of three tiers:

[20] Key considerations related to interpreting evidence of secondary spread are noted in U.S. EPA, 2005b.

- Tier I: Site/Incident Assessment
- Tier II: Exposure Assessment conducted simultaneously with Hazard Assessment
- Tier III: Risk Characterization

At the time of this review, the framework was being evaluated using hypothetical scenarios to characterize risks associated with a range of agents and incidents.

The key components of the framework are comparable to the ILSI (2000) approach; however, the elements within the tiers have been modified to suit incident response needs (Nichols et al., 2006). For example, the exposure assessment step requires

- Characterization of the release (e.g., identification of the organism, time and duration of release; number and location of release points; and mode, mechanism, and medium of release)
- Definition of the contaminated area (derived from modeling the initial zone of release)
- Definition of the exposed population (including their activity patterns and probable exposure scenarios)
- Development and execution of an environmental sampling plan (based on scenario and population data)
- Estimation and prediction of exposure concentrations (define the boundaries of the contaminated area, and estimate exposure levels)
- Estimation of intakes (select exposure models, determine values of exposure factors, and characterize uncertainty and variability)

In the Center's framework, hazard assessment involves identifying the hazard and predicting the health hazards using dose-response modeling, while risk characterization combines the results of the health hazard predictions with the exposure estimates for each exposure scenario.

Each of these tiers poses unique challenges that ought to be addressed to fully implement the framework. Some of the challenges relate to

- Technical and laboratory limitations (e.g., false positives, delays in diagnostics)
- Constraints due to the nature of the bioagent and host populations, environmental conditions, and exposure characteristics (e.g., health effects related to the organism that mimic common conditions such as influenza, lack of relevant and available information or MRAs, multiple routes of exposure, re-aerosolization and transport of bioagents)
- Modeling complexities (e.g., dynamic disease transmission modeling)
- The need to use defaults (e.g., virulence factor activity assessments or infectivity biomarkers)

These and other gaps in MRA methodologies need to be addressed to support homeland security objectives.

4.1.4. Department of Defense

The U.S. Army's Center for Health Promotion and Preventive Medicine has developed a MRA framework (CHPPM, 2006), which builds on the traditional chemical risk assessment approach (NRC, 1983). The focus is on supporting decision-makers in determining "How clean is safe?" The Center's framework has been designed for predictive and not incident response purposes. The four-step approach includes

- Planning and Problem Formulation
- Release Assessment
- Exposure and Infectivity Assessment
- Characterization of Health Impact

Assumptions made and uncertainties noted throughout the application of the framework are described in a table at the end of the MRA.

The first step entails identification of the microbial pathogen and receptor population(s), health endpoints, and development of the analysis plan and risk management options. Assumptions for conducting the assessment are explicitly stated. A substep, Threat

Identification, involves examining the interactions that occur between the pathogen and human populations in a variety of environments.

Release Assessment describes the mechanism by which the pathogen is released and distributed and estimates the rates of release, in order to estimate exposure point concentrations (e.g., the environmental concentrations which receptor populations would experience). This estimation process may be completed for several scenarios, and addresses the range of environmental factors in this fate-and-transport modeling step. Sources of uncertainty are described.

Exposure Assessment estimates exposures among the receptor populations, considering characteristics of the host, pathogen, and environment. Important factors include inhalation rate, exposure time, and internal biological deposition and clearance. The output of this step, with uncertainties described, is a set of estimates of the pathogen concentration within the human receptor.

Another component of the third step of the framework is Infectivity Assessment. This step parallels the traditional dose-response step (NRC, 1983); it evaluates the impacts of the pathogen level in the target organ, considering variability and the sources of uncertainty involved in modeling the pathogen-response relationship. Pathogen factors are more influential in the Infectivity Assessment component of the framework, while host characteristics are the focus in Exposure Assessment. Literature is reviewed, debates noted about infectivity values, and rationales for the choices made are documented. A reference value is calculated, with uncertainties stated, and then used to estimate the risk from exposure to the pathogen. This value is one of the inputs to the next step of the framework.

The last step, Characterization of the Health Impact, integrates the prior steps' outputs by comparing the estimated health impacts to the Infectivity Assessment reference value. The estimates may be expressed in a qualitative manner, rather than quantitative estimates, but uncertainties are described. One qualitative format is a matrix of estimates by hazard probability and hazard severity. This matrix provides decision-makers with a succinct presentation of the range of risks, thereby facilitating their decisions. Decision-makers are further aided by a table of assumptions and uncertainties, allowing them to interpret the matrix with greater insight.

4.2. CANADA

4.2.1. Health Canada

Health Canada published and adopted its risk assessment framework in 2000 (Health Canada, 2000). The framework is based on the U.S. Presidential/Congressional Commission's work (P/C, 1997)[21], because it used an iterative, integrated approach that reflected the interrelationships of actual decision processes (Health Canada, 2000). Health Canada's framework includes a problem formulation step, uses a public health approach, and is intended to address all potential human health risks including microbial pathogens (Jardine et al., 2003).

Health Canada uses a flexible, six-step framework for developing drinking water guidelines, including those for addressing microbial pathogens (Krewski et al., 2004). Although both the traditional four-compartment model (NRC, 1983) and the ILSI, 2000 model are described, neither is pointed to as the preferred approach in implementing Health Canada's paradigm. The six steps are

- Identification (determination as to whether a contaminant should be considered for guideline[22] development)
- Assessment (a science-based risk assessment of potential health risks)
- Evaluation (examination of the feasibility of implementing the recommended guidelines)
- Decision-making and approval (governmental entities approve the decision to set or revise guidelines)
- Announcement and publication (public release of the guidelines)
- Re-evaluation (to be conducted as needed)

[21] Jardine et al. (2003) pointed out that Health Canada's framework is based on the P/C (1997) approach. While no MRA framework reviewed for this paper explicitly cited P/C (1997) as its basis, other MRAs did reflect or use key P/C principles: iteration, inclusion of stakeholders, protection of public health, scientific bases, and risk assessment within a comprehensive risk management approach. WHO has based its recent public health policy guidance on P/C's principles and framework (McLaughlin Centre for Population Health Risk Assessment, University of Ottawa, and World Health Organization, 2005).

[22] In North America and Europe, guidelines typically do not have the same regulatory or enforcement implications as standards. Guidelines are usually developed to improve the quality and consistency of products (such as risk assessments), and are therefore recommended as "best practices." However, standards are requirements that must be met to avoid enforcement actions. WHO (2001) has stated that guidelines provide a scientific rationale on which nations can build standards in their own social, economic, and environmental contexts. In Canada, guidelines are used to provide "a flexible process that must accommodate the diverse needs of various jurisdictions (Health Canada, 1999a)," as cited by Krewski et al. (2004).

Additionally, the paradigm stresses communication throughout the process that public consultations be included as early as the first step (identification). Public input in evaluation is seen as particularly important.

4.2.2. Public Health Agency of Canada

Lammerding (2006) of the Public Health Agency of Canada has described MRA as systematic, structured, and integrative. It is a "modular process" that builds on steps in a chain, such as a food production process; the output of one module serves as the input for the next module in the chain. She provides examples of modular MRAs and discusses different modeling approaches. She also states that it is important to ensure that the MRA level matches the risk management needs. Lammerding's review of microbial risk assessment methods and modeling is an excellent summary, but it does not indicate whether the Public Health Agency of Canada prefers any particular approaches or has adopted a specific framework as policy.

4.3. AUSTRALIA AND NEW ZEALAND

Australia and New Zealand have defined "risk assessment" as "the overall process of using available information to predict how often hazards or specific events may occur (likelihood) and the magnitude of their consequences (adapted from AS/NZS 4360:1999)" (NRMMC, 2006). The purpose of risk assessment is "to distinguish between very high and very low risks so that priorities for risk management can be established" (NHMRC-NRMMC, 2004). The fundamental approach is based on the traditional four-step chemical risk assessment paradigm (NRC, 1983).

4.3.1. Australia

Risk assessments are conducted within a larger risk management framework, based on HACCP principles (Codex, 1997); systems such as ISO 9001 (AS/NZS, 2000); and WHO's unified risk management approach for drinking water, recreational water, and recycled water (WHO, 2001). This framework is described in Australia's *Drinking Water Guidelines* (NHMRC-NRMMC, 2004) and WHO's *Guidelines for Drinking Water Quality* (WHO, 2004b). Australia's risk management framework has 12 steps (or elements), which are organized into four components:

- Commitment to responsible use and management (Element 1)
- Systems analysis and management (Elements 2-6)
- Supporting requirements (Elements 7-10)
- Review (Elements 11-12)

The Systems component contains the risk assessment process (Element 2). However, in the Commitment component, a risk management framework, conceptual model, and plans are developed before the risk assessment process is initiated; this is essentially a planning and scoping step (Element 1). (Figure 4).

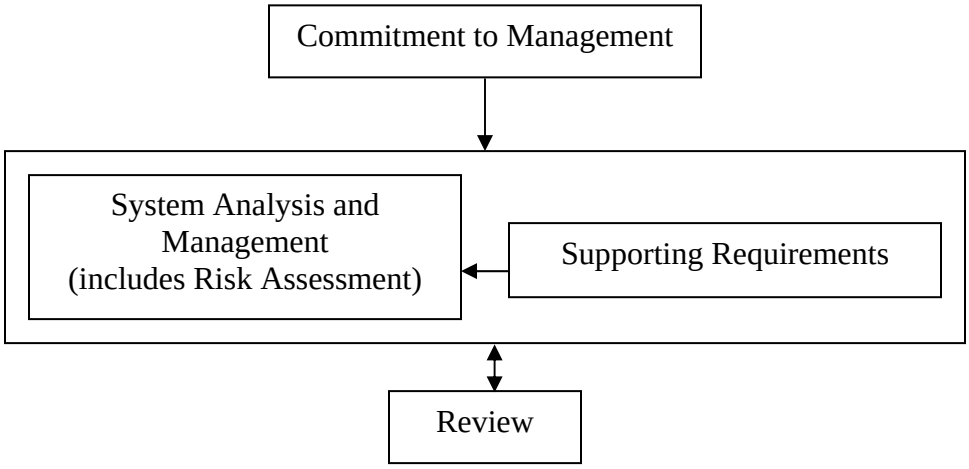


Figure 4. Australia's risk management framework including risk assessment. Sources: Adapted from NHMRC-NRMMC, 2004; NRMMC, 2006

The risk assessment follows the traditional four steps: hazard identification (including a preliminary or screening risk assessment); dose-response; exposure assessment; and risk characterization (labeled risk assessment). The output of the risk assessment process is one or more risk estimates, which may be expressed quantitatively or qualitatively. Qualitative risk estimates (from low to high) may be communicated in a matrix of likelihood and consequence levels. An initial, screening-level risk assessment may be conducted to distinguish between high and low risks. Guidelines and criteria for estimating risks are available for specific sources and end uses (e.g., as in for recycled water in NRMMC, 2006). These guidance materials also indicate that uncertainty, variability, and limitations of the risk assessment need to be discussed and documented (NRMMC, 2006; NHMRC-NRMMC, 2004). Quantitative estimates of the

likelihood of illness are expressed in DALYs to convey the magnitude of disease burden and to provide a benchmark for "tolerable risk."

Other components (Elements 1, 6, and 8) of the framework address risk communication issues; including identification and engagement of stakeholders (1), management of incidents and emergencies through communication and incident response protocols and strategies (6), and two-way forms of community involvement to address longer-term risks (8) (e.g., NRMMC, 2006). These three sections of the guidelines describe general principles for ensuring appropriate types of communication with related agencies, employees, contractors, the mass media, stakeholders, the general public or consumers.

4.3.1.1. *Drinking Water*

The specific issues associated with conducting a risk assessment for categories of pathogens (e.g., bacteria, viruses) are described in broad terms. The probability of community outbreaks relates, for example, to the virulence of the pathogen, consumption rates of consumers, infectious dose of the specific pathogen, and incidence of the infection in the community. Susceptible subpopulations—such as very young, immunosuppressed, sick and elderly people—are considered in microbial risk assessments. Subgroups also include people who have had recent surgery, injury or burns (e.g., groups with compromised defense mechanisms) (NHMRC-NRMMC, 2004).

4.3.1.2. *Recycled Water*

Australia's guidelines for managing risks associated with the use of recycled water address both environmental and health hazards (NRMMC, 2006). Human health risk assessment explicitly deals with multiple microbial pathogen-related risks; risk characterization is described in detail in Appendix 2 of Australia's guidelines (NRMMC, 2006). Susceptible subpopulations are defined using a range of characteristics and thereby are considered in the risk assessment. Tolerable levels of risk are expressed in terms of DALYS (disability adjusted life years) per person per year. Both deterministic and stochastic analyses are considered, and health-based performance targets are calculated.

4.3.2. New Zealand

The New Zealand Food Safety Authority has completed a risk profile, or qualitative assessment, to screen the risks associated with salmonella in whole and pieced poultry (NZFSA,

2004). The framework used to conduct this MRA complied with Codex principles (1999) and followed the order of hazard identification, hazard characterization (dose-response), exposure assessment, and risk characterization.

In the New Zealand risk management framework, risk communication and consultation encircle risk assessment (NZFSA, 2004), but the MRA text does not indicate how these activities are to be conducted.

4.4. FRANCE

Quantitative microbial risk assessments have been conducted by the French Food Safety Agency (Agence Francaise de Sécurité Sanitaire des Aliments). The authors of a quantitative risk assessment of waterborne cryptosporidiosis stated that WHO's recommendations and framework (FAO/WHO, 2002a) were the basis for their work (Pouillot, et al., 2004).

WHO's "global risk assessment model" is presented in the following order: hazard identification, consumption, pathogen emission, exposure, and effect. These components were examined at the individual level. Over 20 assumptions were made to design and implement the model; the impacts of many of these are discussed. The results for *C. parvum* infection are presented on two levels, daily and annual risk estimates, for immunocompetent and immunodeficient populations.

4.5. THE NETHERLANDS

Using a modular process risk model approach, Nauta et al. (2005) conducted a quantitative microbial risk assessment of campylobacter transmitted through several routes of exposure: raw and undercooked foods, pet and farm animals, and recreational and drinking water. The guiding framework for this assessment was a "farm-to-fork" chain, with an exposure module at the "fork" end. The output of this chain became the input for a dose-response model for predicting the annual number of cases of infection and illness in the Dutch population. The authors noted that a qualitative outcome based on the quantitative results may be more appropriate for public health decision-making processes.

4.6. SWEDEN

The National Food Administration of Sweden follows the four-step risk assessment framework, originated by the NRC (1983) and supported by Codex (1999). This framework has been used to conduct a quantitative risk assessment of the exposure and risk of developing

listeriosis from consumption of contaminated ready-to-eat foods, particularly gravad or smoked salmon and rainbow trout (Lindqvist and Westöö, 2000).

4.7. UNITED KINGDOM

Due to increasing sociological, political, scientific, and economic needs, the United Kingdom has been examining microbial risk assessment approaches and applications since the late 1980s (ACDP, 1996). The Advisory Committee on Dangerous Pathogens has defined MRA as "a formal structured procedure for identifying and characterizing microbial hazard and determining the risk associated with it" (ACDP, 1996). Although some of the basic principles are the same, UK experts have stated that MRA involves issues not found in chemical risk assessment.

The committee also laid out an eight-stage approach to MRA, in which Stage 1 requires a problem statement, Stage 2 involves the conduct of the MRA, and Stage 7 addresses risk communication needs (ACDP, 1996). Stage 2 is ordered in a manner similar to the NRC (1983) paradigm. The approach identified host, environment, and pathogen factors that influence the conduct of MRA and noted the importance of principles underlying HACCP and HAZOP (Hazards and Operability) processes. The Committee also described computational models available to conduct portions of MRAs, such as the food micromodel for common food poisoning bacteria. The need to clearly state sources of uncertainty and their impacts on MRA results was noted.

4.8. EUROPEAN UNION

The European Commission has undertaken a number of activities to address and advance MRA issues. Several organizations within the European Union (EU) have published documents describing the framework and bases for microbial risk assessment. Harmonization of risk assessment procedures for quantitative microbiological risk assessment was initiated in the 1990s and culminated in a report (EC, 2000) that serves as the basis for continuing work (e.g., EC, 2003). This report of the Scientific Steering Committee's Working Group on Harmonisation of Risk Assessment Procedures adopted the NRC (1983) paradigm, with a preceding problem definition step. This step included formulation of the risk assessment questions and conduct of a preliminary assessment for planning and scoping purposes. The report also recommended the development of quantitative risk assessment guidelines and common exposure models and scenarios, noted the importance of using epidemiological approaches, and established a Working

Group on Risk Assessment as Applied to Biological Materials, which has focused on bacterial pathogens in foods. The report briefly discussed the four traditional steps of risk assessment as they applied to microbial pathogens, noting that some aspects of pathogen exposures required different approaches.

Another product of the Working Group was a report on quantitative methodologies for exposure assessment[23] in foodborne pathogen risk assessments, which adopted the modular process risk model to represent six basic steps within the farm-to-fork pathway (EC, 2003). The EU's Steering Committee also carries out MRAs on specific topics (e.g., bovine spongiform encephalopathy), with input from several working groups (EFSA, 2005c).

The following two EU organizations have documents describing the framework and bases for microbial risk assessment.

4.8.1. European Commission on Food Safety

The European Commission on Food Safety (ECFS) published MRA principles that adopted the chemical risk assessment steps (hazard identification, hazard characterization, exposure assessment, and risk characterization), but acknowledged that these steps did not have to be completed in a rigid order, because the order be designed to suit the purposes of the risk assessment (ECFS, 1997). The ECFS also adopted a step focused on formulating a statement of purpose as a precursor to implementing the four MRA steps. In another forward-thinking statement, the agency said that the dynamics of both the microbial pathogen (and related toxins) and the host population must be considered in MRA. Risk communication is not explicitly addressed in this document, but a publicly available, clear, transparent, fully documented, and systematically organized report is expected as the final product.

4.8.2. European Food Safety Authority

In an EU workshop conducted in 2000, experts stated that the basic formal steps for MRA include identification/characterization, analysis, and assessment, but that the conduct of each step is heavily dependent on regulatory and cultural contexts (Jardine et al., 2003). The European Food Safety Authority (EFSA) has subsequently published a guidance document relevant for microbial risk assessments (EFSA, 2006b). This manual describes the steps of risk assessment as hazard identification, hazard characterization, exposure assessment, and risk

[23] The definition of exposure assessment used here is "an estimate of how likely it is that an individual or a population will be exposed to a microbial hazard and what numbers of organisms are likely to be ingested" (Lammerding and Fazil, 2000).

characterization. These steps have been implemented in an EU opinion on Ochratoxin A in food (EFSA, 2006c).

EFSA's guidance for risk assessment of genetically modified plants presented the MRA as the traditional NRC (1983) framework, and noted this approach aligns with prior European Commission and Codex policies (EFSA, 2006a; 2006b; 2006c). The guidance includes extended discussion about the characteristics and issues that need to be considered in the hazard identification and hazard characterization steps. Some of the information needed relates to the traits and characteristics that have been modified in the plant, derived food, or feed; details of the genetic insertion or deletion; expression of the genetic insert; genetic stability of the genetically modified plant; information on any toxic, allergenic, or other harmful effects on human or animal health, etc. The exposure assessment step requires information to describe the pathways by which genetically modified plants may be modified in the environment and interact with components of the environment and/or with humans. The risk characterization step considers the genetically modified plant's molecular character compared with naturally occurring varieties, as well as food and feed safety issues and environmental impacts. Although this guidance builds from the traditional NRC framework, it requires the integration of a wide range of ecological and human health concerns.[24]

EFSA guidance on genetically modified plants defines risk communication as "the interactive exchange of information and opinions throughout the risk analysis process as regards hazards and risks, risk-related factors and risk perceptions among risk assessors, risk managers, consumers, feed and food businesses, the academic community and other interested parties, including explanation of risk assessment findings and the basis for risk management decisions" (EFSA, 2006d).

In a separate guidance document issued for transparency in risk assessments, EFSA distinguished between "institutional" and "civil society" stakeholders on the basis that the agency has different legal and legitimate responsibilities to each (EFSA, 2006b). EFSA stated that wide stakeholder involvement, active dialogue, and collaboration are important, but that pre-determined criteria are needed to identify when stakeholders should be involved and on what topics.

[24] This is in alignment with the integrated framework recommended by Suter et al. (2005).

4.9. UNITED NATIONS

Risk assessments for five microbial pathogens have been posted on United Nations-related websites; in some cases, multiple, evolving versions are posted. The pathogens examined to date are

- Campylobacter in chickens and seafood
- Enterobacter in infant formula
- Listeria in ready-to-eat foods
- Salmonella in eggs and broiler chickens
- Vibrio in raw oysters

All of these MRAs start with a distinct hazard identification step and end with risk characterization, while some include a scoping step. Some document the exposure assessment step before the hazard characterization (e.g., chickens in WHO, 2002) and others do not (e.g., seafood in WHO, 2002). There was no obvious reason why this inconsistency should be the case, given that Codex has adopted a risk assessment framework with exposure assessment preceding hazard characterization (Codex, 1999).

The joint initiative between the Food and Agriculture Organization of the United Nations (FAO) and WHO and Codex has defined "risk communication" as an interactive exchange of information and opinions about risk among risk managers, risk assessors, and stakeholders (Codex, 1999; FAO/WHO, 1995). While a few UN agency MRA guidance documents have discussed risk communication (e.g., WHO, 2004b), to date, none of the MRAs completed by United Nations entities have included discussions about risk communication.

4.9.1. Joint FAO/WHO

FAO/WHO have jointly defined MRA as "an objective, systematic evaluation of relevant scientific knowledge to help the risk manager make an informed decision about how to reduce risk posed by a food safety issue," and dynamic and predictive modeling methods are used to estimate public health risks (FAO/WHO, 2006).

Joint initiatives, convened at the request of Codex, have played a crucial role in developing, standardizing, and informing MRA and related guidelines on an international scale. The 1995 Joint Consultation experts recommended that Codex adopt a four-compartment model for biological agents in foods, similar to the NRC approach used for chemical risk assessment

(FAO/WHO, 1995). The steps in MRA were identified as: hazard identification, hazard characterization (including dose-response), exposure assessment, and risk characterization. The FAO/WHO model emphasizes sound scientific bases, as much quantification as possible, clearly stated outcomes, and HACCP-based options for MRA. However, the Consultation recognized that more knowledge and information and a different application of the four-compartment model would be needed to adequately address microbial risks. In the risk evaluation step, prior to risk assessment, the food safety problem is identified and ranked, and the policies needed to conduct the risk assessment are defined; this is equivalent to some scoping and planning steps of other agencies (FAO/WHO, 2000). Sound scientific bases, as much quantification as possible, clearly stated outcomes, and HACCP-based options are noted as the foundations of MRA.

The Joint FAO/WHO Expert Consultation on the Application of Risk Analysis to Food Standards Issues was held in 1995 to provide Codex, FAO, and WHO with advice on practical approaches to risk analysis for food issues, and to promote consistency and transparency in related Codex standards and guidelines. In a later Joint Expert Meeting, it was noted that public health goals (such as appropriate levels of protection) can be achieved when MRAs inspire the public and governments to take appropriate actions. This is more likely to occur when the public and officials have been engaged as stakeholders in the process (FAO/WHO, 2006).

Risk assessment and risk communication, along with risk management, are the three major components of the United Nations' approach to risk analysis (FAO/WHO, 1999). In 1998, a Joint FAO/WHO Expert Consultation addressed risk communication for food-related matters (FAO/WHO, 1999). The convener noted that risk communication occurs throughout the risk assessment and management processes, among all parties involved (including the public), and requires different types and tiers of communication. The consultation produced a list of risk communication goals, such as to promote awareness and understanding of risk analysis issues, contribute to effective information and education programs, involve all interested parties, and strengthen working and mutually respectful relationships. Principles noted to be fundamental to risk communication are transparency and consistency. The Consultation affirmed the importance of pursuing risk communication through a systematic approach, and recommended a number of issues to be considered in planning for crisis and non-crisis conditions. Furthermore, FAO/WHO documentation states that risk assessment results should be made public and communicated to relevant and interested parties (FAO/WHO, 2003b).

4.9.2. Codex Alimentarius Commission

The primary purposes of this intergovernmental organization are to protect human health and ensure fair practices in food trade (FAO/WHO, 1997). Codex is a subsidiary body of the FAO and WHO; it provides an annual forum for dialogue and debate about major, international food safety issues. Through the work of its committees, the Commission establishes international food safety standards and guidelines, develops principles for using risk assessment to identify such standards, and has risk management responsibilities for food in international trade. The World Trade Organization considers Codex opinions representative of international consensus regarding foodborne health risks and controls. Codex initiated a survey of risk assessment methods in 1993, provided guidance for risk analyses of foods in 1994, and has conducted a series of expert consultations on MRA since 1995 (EC, 2000).

The committee that primarily addresses MRA principles, approaches, and related issues is the Codex Committee on Food Hygiene. Codex describes risk analysis as having three major parts: risk assessment, risk management, and risk communication. Codex has adopted a modified form of the chemical risk assessment framework for food-related MRA and incorporated HACCP concepts. The four components in the Codex framework are: hazard identification, hazard characterization, exposure assessment, and risk characterization (WHO, 1999). Like the European Commission on Food Safety, Codex has clearly stated that the dynamics of microbial pathogens (growth, survival, and death) must be accounted for in microbial risk assessments of foods.

Codex defines risk communication as "the interactive exchange of information and opinions concerning risk and risk management among risk assessors, risk managers, consumers and other interested parties" (Codex, 1999). One of the goals of risk communication in Codex processes is to increase the credibility and public acceptability of risk assessment outcomes.

4.9.3. International Office of Epizootics

Aligned with the SPS Agreement and its World Trade Organization responsibilities, this office has addressed MRA related to animals used for foods, and has incorporated risk analysis guidelines in the International Health Code. These guidelines address and provide underlying principles for risk assessment (EC, 2000).

4.9.4. World Health Organization

The WHO Environmental Health Criteria Programme was established in 1973, in follow-up to the UN's Conference on the Human Environment in the prior year. The work conducted by this office contributed to chemical risk assessment strategies, and monographs on the assessment of contaminants in food (EC, 2000).

WHO approaches MRA as part of an overall risk management problem (Codex, 1999). MRA serves a crucial role in risk management paradigms; it is pivotal to ensuring that the quality of synthesized information is high, and that related management options provided to decision-makers are as complete as possible and relevant to the originally defined problem and scope. Several agencies have described generic risk management frameworks (e.g., P/C, 1997; CSA, 1997), but only one has been specific to microbial risks (WHO, 2003a).

WHO's four components for managing microbial pathogens are

- Preliminary risk management activities
- Evaluation of risk management options
- Implementation of the risk management decision
- Monitoring and review

The first step, preliminary risk management, includes the MRA process. Although a problem formulation component may be added (OECD/WHO, 2003), WHO typically uses the traditional four-compartment approach to MRA: hazard identification, hazard characterization, exposure assessment, and risk characterization. A preliminary step—statement of the problem—appears in some WHO guidelines (e.g., WHO, 1999), and the middle two steps (exposure assessment and hazard characterization) are sometimes reversed (see chickens in WHO, 2002b) or are shown as concurrent activities (e.g., WHO, 2002a). The agency's steps to conduct MRA involve (FAO/WHO, 2002a)

1. Identifying the food safety issue
2. Initiating immediate interim decisions
3. Determining the risk profile to enable additional decisions
4. Making the initial risk management decisions
5. Defining the purpose and scope of the MRA
6. Establishing policies for the MRA

7. Commissioning the MRA
8. Interacting during the MRA
9. Presenting the results of the MRA
10. Considering the MRA results

Steps 1 through 4 involve programmatic activities that lay the foundation for the MRA conducted in step 5. Once the food safety issue has been identified (step 1), immediate actions may be necessary to protect the public's health (step 2). An initial risk profile involves a systematic collection of information, which is evaluated to determine what other actions (including MRA) and resources may be needed (step 3). If MRA is required, then the risk manager defines the scope, purpose, and operational policies for its conduct (step 4). In step 5, the risk managers and assessors clarify the MRA goals and specific questions. The questions posed depend on the scope of the problem, specific contexts of the microbial risk issue (e.g., the agent, food and exposure pathways involved), and the intended use of the MRA results. Ensuring that the MRA is conducted in a systematic, transparent, and well-documented manner is essential to step 6. Policies that apply generally to MRA and specifically to the problem to be addressed are identified in this step. When the decision-makers call for MRA, (step 7), the mandate and outcome measures—as well as the roles and responsibilities of risk assessors and managers—are clearly laid out. Although assessors and managers communicate during the MRA (step 8), this communication should be objective and limited to necessary technical information, not policy decisions. Risk assessors are responsible for ensuring that the MRA results are provided in a manner that is relevant, useful, and informative to decision-makers (steps 9 and 10).

In its 2002 assessment of *S. enteriditis* in eggs, egg products, and broiler chickens (WHO, 2002a), WHO used an innovative modification of the MRA component of the ten-step process. By sharing the first two steps of the MRA framework but separating the third where key conditions and issues were different, the joint WHO/FAO assessment gained efficiencies and produced outputs relevant for both foods.

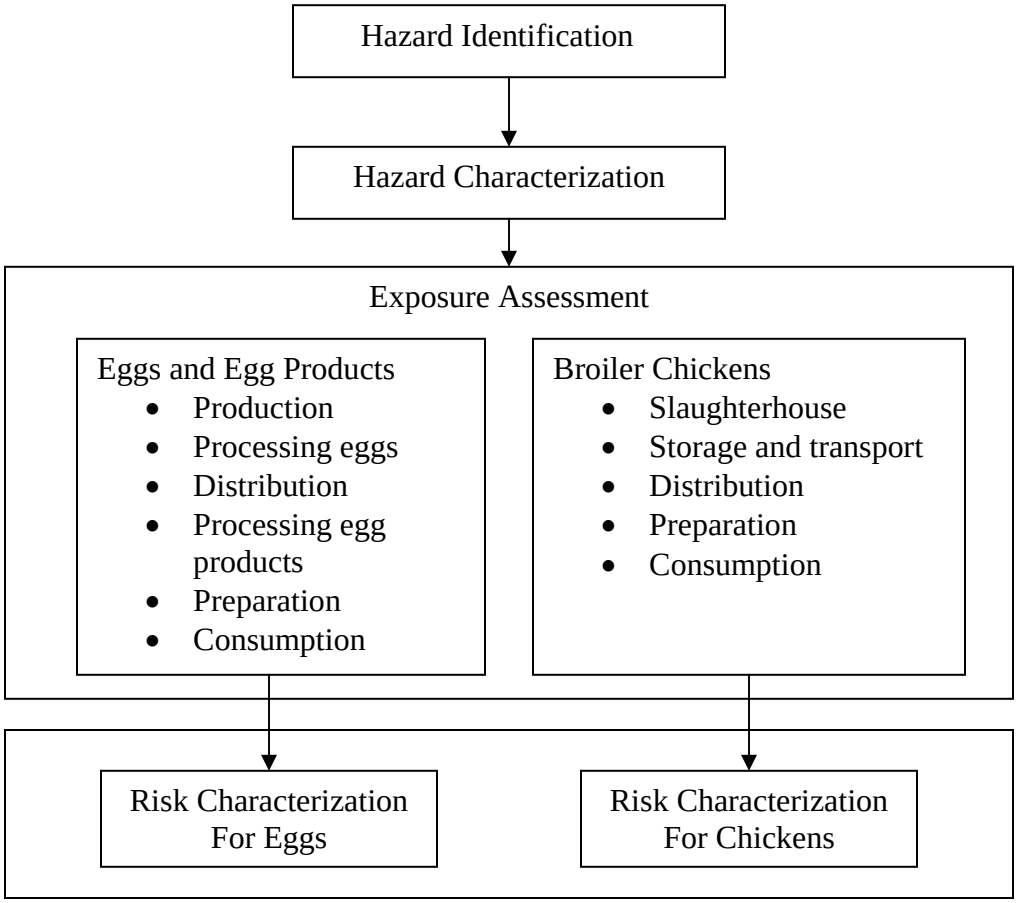


Figure 5. WHO approach to the risk assessment of *Salmonella enteriditis* in eggs and broiler chickens
Source: WHO, 2002a

The 2004 Drinking Water Guidelines (WHO, 2004b) discusses risk communication as an essential part of each step in risk assessment. WHO's stated risk communication goals include raising public knowledge and awareness about issues, and empowering people to participate in decision-making processes and take effective actions. An additional point that is rarely made in MRAs is that understanding the diversity of views is necessary to meet community needs.

5. COMPARISON OF FRAMEWORKS

To elucidate the similarities and differences between governments' and agencies' MRA approaches, at the time of this review, the most recently completed and available MRA for each nation, or agency, when there was more than one completed MRA per government, was selected for study. This review evaluates the type of MRA framework used and the components included in the framework for each MRA. MRAs were found for pathogens in air, drinking water, recreational water, foods (both fresh and processed), biosolids, modified organisms, and intentional uses of microbes.

The purpose of this section is to briefly present and compare completed microbial risk assessments. The analytic focus of this project centered on 12 recently published, government-sponsored MRAs, and one series of EPA MRAs—for biopesticides. Because of the similarities of the MRAs in this series, each set of MRAs was treated as a single MRA approach. Therefore, the unit of comparison in this section is 13 MRA frameworks.

The MRAs compared for this project were

- Cryptosporidium in drinking water (WHO, 2006a)
- Cryptosporidium in drinking water in France (Pouillot et al., 2004)
- Salmonella (non-typhoidal) in poultry (whole and pieces) in New Zealand (NZFSA, 2004)
- *S. enteriditis* in shell eggs and egg products in the United States (USDA, 2005b)
- *S. typhimurium* in three sets of pig-meat products in the United Kingdom (Hill et al. 2003)
- *V. vulnificus* in raw oysters (WHO, 2005)
- *V. parahaemolyticus* in raw oysters in the United States (U.S. FDA, 2005)
- Campylobacter in broiler meat in The Netherlands (Nauta et al., 2005)
- *L. monocytogenes* in fish in Sweden (Lindqvist and Westöö, 2000)
- Eight microbial pathogens in processed wild game in the United Kingdom (Coburn et al., 2005)
- Ochratoxin A in foods (EFSA, 2006c)

- The MRA portion of the economic analysis for the final Long Term 2 Enhanced Surface Water Rule (EPA, 2005b)

An example of the U.S. biopesticides series

- *Streptomyces lydicus* WYEC 108 (U.S. EPA, 2004a)

Note that although other governmental documents have been prepared to initiate MRAs (e.g., the cyanobacterial toxin series produced by the EPA's National Center for Environmental Assessment [NCEA]), these are not complete MRAs and thus did not qualify for evaluation in this review (U.S. EPA, 2006b). The NCEA reviews focus on toxicology, and complete only the hazard identification and dose-response steps of traditional risk assessment.

5.1. OVERALL FRAMEWORK STRUCTURE

Microbial risk assessments involve many factors and complex relationships, including the dynamic aspects of pathogens and hosts and their environment. Such complex systems have networks of factors, feedback loops, and agents that are self-organizing under simple rules. One of the key issues in MRA is how to develop both conceptual and mathematical modeling methods that are sufficient, but not overly complex to address the MRA scope and risk management problem.

"Systems thinking"[25] characterizes complex, dynamic relationships and focuses on emerging and unpredictable outcomes; this approach seems well suited to applications in MRA. Even though increasingly complex MRAs are being conducted, the application of systems thinking to MRA has not yet been explicitly described. One method that can facilitate systems thinking is concept mapping (Trochim et al., 2006), which may be particularly useful in the problem formulation stage of MRA. In concept mapping, multi-disciplinary teams (individually or collectively) brainstorm about what the problem is, what factors affect the problem, and what the boundaries of the problem system are. After participants' ideas are sorted into groups of similar concepts, the team rates each concept group for its relative importance to the problem.

[25] As stated in a recent article, "Systems thinking is a general conceptual orientation concerned with the interrelationships between parts and their relationships to a functioning whole, often understood within the context of an even greater whole" (Trochim et al., 2006). Ecologists use such system-oriented approaches when they define the conceptual model for an ecological risk assessment. In this case, systems thinking involves identifying and characterizing the relationships between the many stressors and endpoints in an ecosystem (i.e., a biotic community and its abiotic environment) (U.S. EPA, 1998).

Through iterations of the data and participants' input, the problem system is mapped into a structured diagram that helps teams identify remaining issues, gaps, and challenges in addressing the problem.

Tools such as risk assessment frameworks and modules[26] help risk assessors organize the complex microbial risk conditions and model dynamic relationships. MRA frameworks provide a broad template to guide the organization of many factors into a series of technical steps and to identify data gaps and appropriate computational methods. Risk assessment frameworks can be constructed on several levels—moving from least to most complex—and applied at the level needed to address the problem. In one analysis of risk assessment frameworks, a broad agreement was found on the three essential parts in risk assessment: identification and possible estimation of the hazard, exposure and/or vulnerability assessment, and risk estimation (IRGC, 2005).

The most basic decision-making model has been described by Drucker (2001) as including three phases: problem definition, analysis, and interpretation. Two of these three components are apparent in both the chemical and microbial risk assessment paradigms (see Table 5). The phase that clearly receives the least attention in MRA frameworks is problem definition. If the generic decision model is used as the benchmark to evaluate the completeness of MRA frameworks, most MRA approaches come up short. They are lacking the first step, which arguably is the most important because it defines what and how the remaining MRA steps are to be conducted.

[26] Although no explicit definition for "module" was found in the MRAs reviewed, WHO has referred to modules in food safety risk assessment guidance as "different areas along the food chain" (FAO/WHO, 2002a). In MRAs, module tends to refer to self-contained units that perform a specific task or function within an overall problem system. Typically, a module is both a distinct conceptual and mathematically modeled unit that produces an output (e.g., pathogen concentration distribution), which is then used in later steps, such as the exposure assessment, of an MRA (e.g., USDA, 2005b).

Table 5. Microbial risk assessment framework structures compared with the basic decision-making model

	Frameworks			
Steps in the Basic Decision-Making Model	**NRC**	**Modified NRC without explicit problem definition**[27]	**Modified NRC with a form of problem definition**	**ILSI**
Problem Definition			Included as problem formulation, problem statement, or scoping step	Problem formulation
Analysis	• Hazard identification • Hazard characterization • Exposure assessment	• Hazard identification • Hazard characterization • Exposure assessment	• Hazard identification • Hazard characterization • Exposure assessment	Analysis • Exposure characterization • Human health effects characterization
Interpretation	Risk characterization	Risk characterization	Risk characterization	Risk characterization
Sources Drucker, 2000	NRC, 1983 WHO, 1995 Haas et al., 1999 Lindqvist and Westöö, 2000 U.S. EPA, 2004a NZFSA, 2004 U.S. EPA, 2005b EFSA, 2006c	Sobsey et al., 1993 Medical Research Council Institute for Environment and Health, 2000 USDA, 2001 FAO/WHO, 2003b	ECFS, 1997 Codex, 1999 WHO, 1999, 2004, 2005, and 2006a U.S. FDA, 2001 U.S. FDA/CFSAN 2005 OECD/WHO, 2003 Pouillot et al., 2004 Nauta et al., 2005 USDA, 2005a and 2005b NRMMC, 2006	ILSI, 2000

Note that Coburn et al. (2005) could not be classified due to the limitations of the documentation. It is likely that this MRA was a modified NRC framework with a problem statement.

Most MRAs do not acknowledge problem formulation ("problem definition" in the basic decision-making model) as a step in the assessment process, but do have a section that states the purpose of the assessment [28] before describing the first recognized step—hazard identification. The purpose may also include comments about the scope of the problem (time, place) or questions to be addressed. Similar to EPA's ecological risk assessment framework (U.S. EPA, 1992), the components of problem formulation in MRA may include characteristics of the

[27] Problem definition (the generic decision-making term) may include problem formulation (U.S. EPA, 2005a), scope or focus, a statement of purpose, a list of risk managers' questions, goals, objectives, plan for conducting the MRA, regulatory or other contextual material, major factors or issues to consider, assessment endpoints, and/or a conceptual model.

[28] Note that problem formulation and statement of the problem are not the same thing. Problem formulation often encompasses more insightful tasks, such as planning and conceptual modeling, than does developing a problem statement. However, problem formulations do not always have the same components, and are not conducted in a uniform manner (EPA, 2003).

pathogen, adverse health effects, endpoints of the MRA, and the conceptual model to guide the MRA.

Elements of hazard identification fit either in "problem definition" or "analysis," but the hazard characterization and exposure assessment steps are clearly within the analytic step of basic decision-making frameworks, and the interpretation step is the same as risk characterization.

The ILSI model follows the basic decision-making model more closely than does the traditional risk assessment approach. In the case of the ILSI model, "problem definition" is labeled "problem formulation"; "analysis" has the same name (with two major subcomponents: characterization of exposure and characterization of human health effects); and "interpretation" is identified as "risk characterization."

Each MRA is publicly available and is supported by technical documentation with varying levels of detail (Table 6). The discussion of the similarities and differences among the frameworks and components used in the MRAs below is based on the publicly available documentation.

Most MRAs had some form of a problem definition. However, two (NZFSA, 2004; Coburn et al., 2005) were qualitative risk assessments. They had particularly general statements of purpose (to provide contextual and background information for decision-makers) and identified the food safety issue (the first step in "risk evaluation") before the NRC framework was used on a screening level. In the NZFSA framework, risk evaluation includes the following sub-steps, with the first sub-step preceding the preliminary MRA:

- Identification of the food safety issue
- Establishment of a risk profile (conduct of the preliminary MRA)
- Ranking of the food safety issue for risk management
- Establishment of risk assessment policy
- Commissioning of a risk assessment (conduct of a full MRA, to the extent that appropriate data and information are available)
- Consideration of the results of the risk assessment

All MRAs used the traditional risk assessment steps (NRC, 1983), but in different orders to suit their particular risk management needs. The structural and component similarities and differences among these MRAs are described in section 5.2.

Table 6. Type and level of component detail available for government-sponsored MRAs

		Problem Definition		***Analysis***		***Interpretation***
Author, Date, and Environmental Category	**Type of Framework**	**Problem Formulation**	**Hazard Identification**	**Hazard Characterization**	**Exposure Assessment**	**Risk Characterization**
Lindqvist and Westöö, 2000 Processed food	Modified NRC with problem definition	Brief statement of objective	Brief description	Moderate detail, including susceptible subgroups	Brief section	Brief probability of illness and annual number of cases
Hill et al. 2003 Processed food	NRC	Brief statement of purpose	Brief description	Moderate description	Extensive detail	Estimates of risk and annual number of cases
EPA, 2004 Modified organisms	NRC	General description	Moderate description	Noted by each route of exposure	Conducted by each route of exposure	Brief statements for each route of exposure
NZFSA, 2004 Processed foods	Modified NRC with problem definition	Identification of the issue, preliminary MRA, planning steps	Descriptions of pathogen and food matrix	Brief section	Focused on pathway of exposure	Description of health effects and qualitative estimate of risk
Pouillot et al., 2004 Drinking water	Modified NRC with problem definition	Statement of purpose	Moderate description	Discussion for both immunocompetent and immunodeficient populations	Moderate description	Probability of infection and then of illness – daily and annual risks estimates
Coburn et al., 2005 Processed food	Unclassifiable due to limited documentation	General question stated	Not included	Not included	Focus of the brief article	Qualitative, relative risk outcome by microbial pathogen
EPA, 2005b Drinking water	NRC	Discussion of purpose, scenarios and approaches	Description of adverse health effects related to the pathogen, subpopulations, water systems	Extensive description and bases for dose-response with three components	Extensive descriptions of pathogen distribution, water consumption, and populations affected	Quantitative estimates of risk of annual illness and death rates on individual and population scales – secondary spread discussed
FDA, 2005 Processed foods	Modified NRC with problem definition	Brief scope, context, objectives, and MRA questions	Description of pathogen, at risk populations, related health effects, etc. with data sources	Fairly brief but includes data limitations and assumption sections, also a very detailed appendix	Diagram of modular approach, and data selection and criteria (with tables)	Description of the output, uncertainty, sensitivity analysis, and model validation

		Problem Definition		*Analysis*		*Interpretation*
Author, Date, and Environmental Category	**Type of Framework**	**Problem Formulation**	**Hazard Identification**	**Hazard Characterization**	**Exposure Assessment**	**Risk Characterization**
Nauta et al., 2005 Processed food	Modified NRC with problem definition	Problem description	Moderate description	Fairly brief section	Extensive "farm-to-fork"	Brief discussion with focus on interventions
USDA, 2005b Processed foods	Modified NRC with problem definition	Purpose, scope, list of risk managers' questions	Brief descriptions of pathogen and related disease	Describes data sources, dose response, and estimates for a range of effect severity	Extensive sections for shell eggs and egg products	Extensive sections for shell eggs and egg products, and includes sensitivity and scenario analyses
WHO, 2005 Processed foods	Modified NRC with problem definition	Scope, context, and objectives presented	Brief description	Focused on dose-response and public health focus, additional material in an appendix	Three module structure, simulations, model validation, and appendix	Brief description
EFSA, 2006c Foods	NRC	General description	Moderate discussion	Extensive toxicological review	Moderate description with data	Brief statement with mention of infants and children
WHO, 2006a Drinking water	Modified NRC with problem definition	Detailed formulation conducted after Hazard Identification	Detailed description of the pathogen and its infectivity	Detailed dose-response in the Effect Assessment step	Detailed consideration of detection and monitoring; less detail about consumption	Novel inclusion and description of three case studies demonstrating the MRA's practical value

5.2. INDIVIDUAL FRAMEWORK COMPONENTS

Each MRA step may develop concepts and implement quantitative models to varying levels of depth, depending on the MRA objective and the availability of data to support detailed mathematical models. In the more detailed cases, MRA documentation is more likely to refer to modules, particularly in the exposure assessment step. In this step, more complex modeling is more commonly being seen, and dynamic functions between agents and hosts are mathematically modeled.

Before exploring the similarities and differences among the MRAs, descriptions of each component of the MRA frameworks follow (primarily based on definitions listed in EPA, 2005a). The components are scope and framework, problem formulation/statement, feasibility, conceptual model, analytic plan, plus the four traditional components that are associated with the NRC model: hazard identification, hazard characterization, exposure assessment, and risk characterization. The final component is risk communication.

While the European Commission, Codex, and WHO also require a statement of purpose and most U.S. MRAs include a statement of the scope, it is important to note that these scoping concepts are not the same. A statement of purpose is usually limited to the overriding goal that risk managers want to achieve (e.g., rank ordering a set of risks). A statement of scope includes both the managers' questions and the physical, geographic scale of the issue. Codex uses a risk profile step that includes analysis to describe the microbial food safety problem, its scenario (processing, handling, etc.), its contexts (social, cultural, economic, etc.), and a feasibility assessment. If the MRA scope is clear and the MRA is feasible, a conceptual model and management plan need to be in place before the first MRA step—hazard identification—is attempted. In some cases (e.g., WHO, 2006a), scoping is completed as part of or after the hazard identification step.

Risk assessors often use the concepts of problem formulation and problem statement interchangeably, but as the science evolves, problem formulation is increasingly taking on a broader meaning—and often encompasses the problem statement. In a specialty workshop, problem formulation in MRA was defined as "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" (ILSI, 2000). Among definitions for the initial stage of risk assessment (U.S. EPA, 2005a), problem formulation is the most comprehensive concept. MRA problem formulation was described in an EPA workshop (EPA, 2003) as involving several sub-steps, requiring consideration and description of

- Concerns that brought the issue to attention

- Risk management activities
  - Problem statement
  - Objective of the MRA
  - Questions to be addressed

- Risk assessment feasibility
  - Preliminary analysis

- Development of the conceptual model and narrative

- Development of an analytic plan

Problem formulation entails both the fundamental questions to be addressed and a preliminary assessment as to whether a relevant MRA can be conducted. The ILSI model (2000) is the only MRA framework that explicitly calls for a problem formulation step. As problem statements have been more commonly used in microbial risk assessments, this review will also use that terminology, although the methodology appears to be evolving to adopt the broader concept of problem formulation.

1) Problem statement. While the ECFS has called for the routine use of problem statements, FDA and WHO have sometimes explicitly included the "statement of the problem" in their guidelines (Dennis et al., 2001–2002; WHO, 1999). Clear description of the MRA objectives and the risk management questions to be addressed are important parts of defining and scoping the MRA. Additionally, identification of the population and/or subpopulations of concern is essential. Specific groups may be of interest because they could have higher or more frequent exposures, genetic or other predisposing risk factors, or behaviors that would increase the likelihood for their contact with the pathogen.

2) Feasibility. Conducting a preliminary analysis can help the risk assessor identify data and resource needs to implement a quantitative MRA. A preliminary analysis may identify logistical issues, including clarification of roles, responsibilities, and communication procedures.

3) Conceptual model. A conceptual model is a written or visual representation of the predicted relationships between pathogens and exposed populations. It may be based on working hypotheses, supported by preliminary data and information, and used to organize the way the MRA is conducted. The model depicts the purpose, scope, and scale of the MRA; identifies variables and data needed to

conduct the MRA; and can serve as a preliminary or exploratory risk assessment. When comprehensive problem formulation is used, the development of a conceptual model can provide new insights for the risk assessment team, allowing them to understand issues, contributing factors, and data sources beyond their expertise and experience. A systems approach to developing the model (Trochim et al., 2006) can more readily identify gaps in knowledge and information and recognize the feasibility of implementing a full MRA more rapidly.

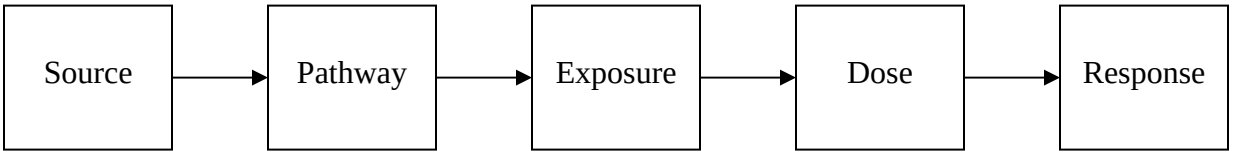
A conceptual model (e.g., a source-pathway-receptor or "farm-to-fork" model) is developed early in the process, but only to the level necessary to address the MRA's purpose. The model should guide risk assessors in

- Ensuring that all possible exposure routes have been considered and explicitly described
- Identifying the types and sources of data needed to conduct the MRA
- Ensuring that the right questions are being asked
- Communicating effectively with risk managers
- Ensuring transparency of the MRA process and bases

An example of a simple conceptual model is presented in the upper portion of Figure 6.

4) Analytic plan. The risk manager develops this plan after a feasibility assessment and before a full MRA is conducted. Risk managers determine whether the MRA is needed, required resources are available, and data and information needed to conduct the MRA are accessible. Once these decisions are made, a plan is laid out for the conduct and outcome of the MRA. An analysis plan may include a list of the risk managers' questions to be addressed, goals, objectives, deliverable products, and timelines, as well as policy and operational guidance.

Pathway Model



MRA Steps

Figure 6. Source-to-response paradigm aligned with relevant MRA steps based on the NRC framework.

The four fundamental steps of traditional risk assessment (NRC, 1983) are commonly used in MRA frameworks. Briefly, the steps are

1) Hazard identification. This term refers to the process used for determining whether a microbial pathogen can cause adverse health effects in humans and what those effects might be. Sometimes characteristics of the pathogen are placed in this MRA step.

2) Hazard characterization. This step describes the potential adverse health effects attributable to a specific pathogen; the mechanisms by which the pathogen exerts its effects; and the associated dose, route, duration, and timing of exposure. This step often includes calculating the dose-response relationship between pathogen exposures and the extent of adverse outcomes among the exposed population.

3) Exposure assessment. This step is used to identify the pathways by which pathogens may reach individuals, estimate the extent of pathogen exposure among humans, and estimate the likely number of persons exposed. A simple pathway model is presented in the upper portion of Figure 6. The output of this step is typically the estimate of the magnitude and/or probability of human exposure to the pathogen or microbial toxin of concern.

4) Risk characterization. The final step of risk assessment is an integrative step that involves the "estimation of the likelihood of adverse human health effects occurring as a result of a defined exposure to a microbial contaminant or medium" (ILSI, 2000). This step is universally used as the last step in risk

assessments. Descriptions of the modeling assumptions, uncertainties, and variability, along with possible risk management options, are also included in this step.

5) Risk communication. Risk communication as a part of risk analysis is widely recognized as the open, interactive exchange of information and ideas about risk. When conducted effectively, risk communication is a strategic component of risk analysis, clearly based on knowledge, not guesses, about stakeholders' interests and priorities (CSA, 1997). Few MRAs presented in this review mentioned risk communication issues.

5.3. SIMILARITIES AMONG MICROBIAL RISK ASSESSMENTS

5.3.1. Scope and Framework

Scope. The scope of most MRAs conducted to date has been focused on specific places (e.g., Soller et al., 2003), foods (e.g., U.S. FDA, 2005), or pathogens in a limited number of foods (e.g., USDA, 2005b). Among the 13 MRAs reviewed in depth, all but one focused on a specific pathogen (e.g., salmonella, vibrio, cryptosporidium). Several MRAs investigated the impacts of a variety of environmental conditions (e.g., U.S. FDA, 2005) or a variety of foods (e.g., Coburn et al., 2005; USDA, 2005a).

Framework. Most organizations that have published MRAs have used the framework of the traditional chemical risk assessment paradigm (NRC, 1983). For food-related MRAs, organizations including USDA, FDA, ECFS, WHO, and Codex tend to use a modification of the chemical risk assessment framework (e.g., U.S. FDA, 2003a; WHO, 2002). In implementing the framework, teams have developed increasingly complex mathematical models.

Among the MRAs studied in depth in this report, five (U.S. EPA, 2005b; U.S. FDA, 2005; U.S. EPA, 2004a; NZFSA, 2004; Hill et al., 2003) followed the same order as the traditional NRC (1983) framework: hazard identification, hazard characterization, exposure assessment, and risk characterization. Six (EFSA, 2006c; WHO, 2005; Nauta et al., 2005; USDA, 2005b; Pouillot et al., 2004; Lindqvist and Westöö, 2000) reversed the middle two steps in this framework, and one (WHO, 2006a) conducted the steps in a unique manner, as described in section 5.4.2. The incomplete documentation in Coburn et al. (2005) made the application of the full framework indeterminable.

5.3.2. Components

FDA and WHO have described the essential parts of each MRA step, shown in Table 7 (U.S. FDA, 2003a; WHO, 2002). Codex and ILSI have captured most of the important elements needed to conduct MRAs (see Appendix 7 of Yoe, 2003), but have not always been clear about the details of how to implement their approaches.

Table 7. Steps in the FDA and WHO frameworks

1. Statement of the problem
a. State clearly the specific problem and scope to be addressed
b. Define the nature and form of the MRA output and output alternatives
c. Create a preliminary model "from farm to fork"
2. Hazard identification
a. Identify the microorganisms or microbial toxins of concern
b. Determine relevant sources of data (such as clinical studies, epidemiological studies or surveillance, laboratory studies, etc.)
c. Gather evidence about the pathogen, its presence in foods, and the adverse health effects (including severity and subpopulations at risk) associated with human consumption of contaminated foods
3. Exposure assessment
a. Define the actual or expected extent of human exposure
b. Determine the scope and frequency of food contamination based on factors such as the microbial ecology of the foods (or matrices) of concern, potential for cross-contamination from contaminated to uncontaminated objects, sanitation and controls in production processes, methods of food handling and packaging, temperatures during storage and preparation, etc.
c. Assess characteristics of consumers (e.g., demographics, behaviors, knowledge, perceptions of food hazards, prior illness, etc.)
d. Examine patterns of consumption by seasonality, region, etc.
e. Describe clearly the pathway from production to consumption
f. Consider using scenarios to identify variations in exposures
g. Estimate the level of pathogens and the probability of their occurrence in foods at the time of consumption
4. Hazard characterization
a. Determine the severity and duration of adverse health effects
b. Examine potentially important characteristics of the microbe of concern (e.g., its ability to replicate, virulence and infectivity, potential for secondary and tertiary spread among hosts, time course from infection to the range of illness outcomes, impact of food attributes on the pathogenicity of the microorganism)
c. Evaluate the importance of host characteristics (e.g., integrity of

physiological barriers, factors that influence susceptibility and time course from infection to illness, population characteristics)
d. Estimate the dose-response relationship, clearly noting the endpoints used for response (e.g., infection, illness)
e. Examine the shape of the dose-response relationship and validate with real world data when possible
f. Consider the importance of severity and duration of disease
5. Risk characterization
a. Integrate the prior three steps using conceptual and computational models to develop a risk estimate
b. Estimate the likelihood and severity of adverse heath effects in a given population
c. Describe the impacts of the assumptions and sources of uncertainty and variability embedded in the estimate
d. Critically evaluate the strengths and weaknesses of the data used (e.g., comment on the weight of the evidence integrated)

The data in this table were merged from numerous sources, cited in the Reference section and in Parkin (2007).

The following component-specific observations are derived from the 13 MRAs examined in detail for this project:

1) Problem statement. Nine of the 13 MRAs (see Table 6) included some type of problem statement. Most included a statement of purpose, and three included a section to describe the scope of the MRA.

2) Feasibility. All of these MRAs omitted documentation of any feasibility assessment that was done prior to conducting the MRA. Little mention was given to issues of data access and availability, although some like EPA (2005b) discussed data sources and their strengths and weaknesses. Some noted data quality issues that limited the nature of the MRA; e.g., the Coburn et al (2005) MRA was qualitative due to the lack of quantitative data.

3) Conceptual model. More detailed MRAs (e.g., U.S. EPA, 2005b; Nauta et al., 2005; USDA, 2005a; Hill et al., 2003) provided extensive documentation of the modeling approaches, components, and underlying concepts. These multi-step models were made up of a series of mathematical models that fed outputs into the next module.

4) Analytic plan. Analytic plans for the MRAs reviewed for this project typically were not presented in the publicly available documentation.

A comparison of the traditional risk assessment steps yielded the following observations:

1) Hazard identification. Among the MRAs reviewed, this step showed the least variation in content. The assessors consistently characterized aspects of the pathogen, its traits, and transmission

routes that make it infective to humans. Typically, this step notes the pathogen's life cycle, virulence, and factors that influenced the pathogen's infectivity.

2) Hazard characterization. All MRAs described host characteristics and disease outcomes, and modeled the dose-response pathogen-host relationship in this step. Most that conducted quantitative MRAs used the beta-Poisson model to calculate the probability of adverse health outcomes (e.g., WHO, 2006). EPA (2005b) used an Exponential Dose Response Model that resulted from combining two probability functions (a Poisson probability distribution of infection given pathogen ingestion and a binomially distributed probability of infection given the dose ingested). Additionally, the step included all described pathogen characteristics that were particularly significant to implementing the model (e.g., Nauta et al., 2005).

In this step, the MRAs that examined processed foods discussed characteristics of food matrices that could influence the shape of the dose-response curve (e.g., U.S. FDA, 2005; USDA, 2005b; WHO, 2005).

Notably, three MRAs provided appendices detailing their dose-response procedures and outcomes; FDA's provides the most detail of all MRAs reviewed (U.S. EPA, 2005b; U.S. FDA, 2005; WHO, 2005).

Coburn et al. (2005) did not include this step in their brief MRA article.

3) Exposure assessment. In 10 of the MRAs, this step was the most extensively documented. Risk assessors used this step to effectively identify and model the complexity of the pathogen pathway and routes of exposure. For example, in the WHO (2005) risk assessment of *V. vulnificus* in raw oysters, the microbe's ecological conditions, growth, and survival characteristics were discussed. EPA (2004) was the only MRA that presented data for numerous routes of exposure. In most cases, numerous factors could affect the outcome of the exposure assessment step, and considerable data needs had to be met.

In most of the MRAs, the exposure assessment presented and described data on the human consumption of water or foods that conveyed pathogens of concern. Distributions of consumption were typically provided and when data were available, differences in consumption patterns were described. The data in this step are essential to characterizing the pathogen-host interface and to producing a useful outcome for risk characterization. Graphing pathways and constructing models for modules within those pathways facilitated organization of the complexities (e.g., USDA, 2005b).

One MRA (Lindqvist and Westöö, 2000) did not provide much detail for this step.

4) Risk characterization. All of the MRAs described their modeling approaches and outputs in this section. Furthermore, although there are differences in level of detail, all agencies used this step to present, describe, and interpret their modeling results. Risk management options were also noted, but in different ways.

It is in this step that most MRAs evaluated and described the sources of uncertainty and variability that affect the final MRA estimate of illness. Uncertainty is the result of unknown and unknowable errors in the data used in the MRA. Variability is the result of inherent heterogeneity in the data inputs (WHO, 2006a).

5) Risk communication. The MRAs reviewed had little, if anything, to say about risk communication.

5.4. DIFFERENCES AMONG MICROBIAL RISK ASSESSMENTS

5.4.1. Scope and Framework

Scope. The MRAs reviewed handled scoping issues in different ways—in statements of purpose, risk profiles, or problem formulation steps. The 13 MRAs reviewed typically had a national scope, but few addressed place and time explicitly. Furthermore, few addressed the risks to susceptible subpopulations (e.g., EFSA, 2006c; U.S. EPA, 2005b; Pouillot et al., 2004).

Framework. While most organizations have adopted the traditional chemical risk assessment framework or a modification of it for microbial risks, the EPA National Homeland Security Research Center office has used the ILSI (2000) paradigm as the basis for its incident response assessments (Nichols et al., 2006). Their process begins with problem formulation and ends with risk characterization; the differences appear in the analytical phase. The Center's exposure assessment and hazard assessment steps involve many of the elements that appear in the analysis phase of the ILSI paradigm. Elements within each of these steps, however, have been aligned differently than in the exposure characterization and human health effects characterization steps of the ILSI framework. Additionally, exposure assessment requires a conceptual model that is generally similar to source-pathway-receptor approaches, but includes sampling for incident response contexts.

Among the MRAs studied in detail, WHO (2006a) modified the traditional NRC steps in a unique manner: problem formulation was documented after hazard identification.

5.4.2. Components

ILSI (2000) and Codex (1999) have listed many elements that need to be considered in MRA steps. These elements have been reviewed and compared by Yoe (2003); there are many similarities in what elements to include, but terminology varies. Codex is more inclusive in the hazard characterization step (e.g., regional, behavioral, and ethnic concerns are more developed), while ILSI includes more elements for dose-response (e.g., specificity of the organism strain and virulence and use of surveillance and outbreak data). Yoe and others have noted that elements are repeated in several steps in the ILSI framework, potentially causing confusion for some risk assessors. Others have seen this redundancy as supporting flexibility in implementation, or demonstrating an ad hoc approach to MRA (Buchanan et al., 2000).

Components within general MRA frameworks are not typically defined, but may be revealed by examining MRAs published by agencies. For example, elements of problem formulation were identified in some steps (e.g., hazard identification), but generally the MRAs reviewed did not include problem formulation. These differences reflect the current *ad hoc* application of frameworks for MRAs (Yoe, 2003)..

The following component-specific observations are derived from the MRAs examined in detail for this project:

1) Problem statement. The cryptosporidium MRA (WHO, 2006a) was the only one that included an explicitly identified problem formulation step; this comprehensive step followed the hazard identification step. After describing the pathogen's characteristics that make it infective to humans, the problem formulation focused on describing events and disease outbreaks in which waterborne cryptosporidium resulted in adverse human health events. This MRA also examined data from sanitary surveys and historical monitoring systems to describe features of specific sites that contributed to hazardous events and outbreaks.

2) Feasibility. Some consideration of the populations of interest was given early in MRA articles and reports. While the hazard characterization step usually described characteristics of at-risk populations (e.g., U.S. EPA, 2005b; WHO, 2005), the exposure assessment step noted factors and behaviors that could contribute to increased risks. These populations were usually described in qualitative, rather than quantitative terms. A few MRAs included data for subpopulations (e.g., Pouillot et al., 2004; Lindqvist and Westöö, 2000).

3) Conceptual model. Several of the MRAs presented modular schematics that helped organize and explain the assessment's components, contributing factors, and calculations (U.S. FDA, 2005; Nauta et al., 2005; USDA, 2005b; WHO, 2005). USDA offered a schematic early in the documentation (Figure 1-1 on page 11 of USDA, 2005b) that showed the MRA steps and the factors to be addressed in each step. More detailed schematics are presented and discussed in each of USDA's MRA steps. Both FDA and USDA described their modules extensively, although USDA does not use "module" in reference to the compartments or separate mathematical models in its MRA. These modules are described further in section 5.5.2.

WHO's raw oyster MRA (WHO, 2005) presented a conceptual model with three modules—Harvest, Post-Harvest, and Public Health. This schematic (Figure 1 on page 22 of WHO, 2005) is offered in the Interpretative Summary, as well as in the exposure assessment step. In both cases, it helps the reader follow the text and grasp the impact of the many factors considered in modeling the health risk.

Lindqvist and Westöö (2000) provided a schematic of their conceptual model, with some equations linking components of the model.

4) Analytic plan. Although some of the MRAs generally described their approach (e.g., U.S. FDA, 2005), only one provided an explicitly labeled "modeling plan"; this was a detailed description for a probabilistic analysis of shell eggs (USDA, 2005b). The plan described the components of the model (see section 5.2); the inputs for assessing pathogen concentrations throughout the model; the means to handle uncertainty; and other aspects of modeling.

Observations about the differences in application of the four steps in the traditional risk assessment framework follow:

1) Hazard identification. In this step, some of the MRAs (e.g., NZFSA, 2004; WHO, 2004b; WHO, 2006a) identified hazards. These and three more MRAs (U.S. EPA, 2004a; U.S. FDA, 2004; EFSA, 2006a) described pathogen pathways in different foods, processes, and/or geographical regions.

FDA (2005) provided the most extensive description of the possible sources of contamination in this step.

In one drinking water MRA (WHO, 2006a), a detailed hazard identification step described the pathogen's characteristics (e.g., life cycle, prevalence, and routes of transmission), ability to be transmitted in water (e.g., environmental sources, resistance to chemical treatment and filtration by

water systems, persistence in drinking water), and the characteristics that make it pathogenic to humans (e.g., infectivity, shedding).

2) Hazard characterization. The WHO raw oyster MRA (2005) presented its Public Health module (including dose-response calculations) in the hazard characterization step, which followed exposure assessment in the documentation. The step described the pathogen's virulence, host susceptibility factors, health behaviors, characteristics of oysters as food matrix, and adverse health outcomes. The dose-response relationship was modeled using a beta-Poisson approach. Furthermore, impacts of modeling assumptions, uncertainty, and variability were analyzed and described here, rather than in the risk characterization step.

EPA (2005b) presented an analysis of several dose-response models, and compared them to determine which approach was most suitable. The description of these models and their relative merits for the MRA purpose is extensive and informative. Furthermore, this MRA used data on infectivity from numerous published studies to estimate a probability distribution for infectivity and used morbidity and mortality factors to estimate, respectively, the risks of illness given infection and the risks of death given illness.

3) Exposure assessment. Three of the MRAs (U.S. FDA, 2005; Nauta et al., 2005; USDA, 2005b) presented detailed modules, subcomponents, schematics, and mathematical models to characterize the changes in pathogen concentrations as the microorganisms moved through source-to-host pathways. The most complex set of modules was developed in the USDA (2005b) MRA of salmonella in shell eggs and egg products. The complexity resulted in part because these two types of foods do not have the same farm-to-fork pathway; consequently, each had to be described, modeled, and discussed separately. For example, the farm-to-fork model described in this step had eight modules that were mathematically modeled (See section 5.5.2.)

The WHO MRA of raw oyster risks (2005) modeled harvest and post-harvest processes; included simulations of differing source, environmental, and handling conditions; and preserved data for the purpose of validating the model.

WHO's MRA (2006a) detailed assessments of exposures and effects presented in two separate steps. This MRA also provides insights into how to obtain data necessary to conduct MRAs. First, the exposure assessment section presents data for and describes the methods by which cryptosporidium is detected in water, monitored in treated and untreated drinking water supplies, and removed by treatment processes. Limitations of treatment, monitoring, and laboratory methods are discussed. Patterns and a

statistical distribution for human consumption of drinking water are also detailed. Second, in the effect assessment step, the host characteristics (including susceptibility factors) are presented, adverse heath effects described, and the dose-response relationships for four strains of cryptosporidium (IOWA, TAMU, UCP, and Moredun) are determined. The evidence basis for effects assessment includes human feeding trials, theories, evidence about host and pathogen factors, and factors that affect the probability of illness following infection. This last issue is important because not all infections lead to clinically diagnosed illness, while some infections (e.g., *C. jejuni*) can result in long-term sequelae.

EPA's exposure assessment of cryptosporidium in drinking water relied on the distribution of the pathogen in finished water, distribution of individual consumption of drinking water and days of exposure, and estimated numbers of the populations served by affected water systems (U.S. EPA, 2005b).

4) Risk characterization. In this step, most MRAs (e.g., U.S. EPA, 2005b; U.S. FDA, 2005: USDA, 2005b) discussed uncertainty and variability, some conducted sensitivity and scenario analyses, and some interpreted the impacts of uncertainty and variability on the MRA outputs. As noted below, however, FDA's detailed appendices provided additional valuable information for understanding how these issues were examined and interpreted (U.S. FDA, 2005).

In risk characterization, WHO (2005) used seasonal variations in water temperature to calculate the annual variation in risk from *V. vulnificus* in raw oysters, and to predict the annual number of illnesses that would result. Additionally, this step presented data describing the impacts of a variety of geographic settings and public health interventions to reduce these risks.

Like most MRAs, based on the outcomes of all prior steps, WHO's drinking water MRA (2006a) presented an integrated assessment of the risk from waterborne cryptosporidium. However, this document provides additional value to decision-makers by describing a tiered approach to risk management; it provides three cases to demonstrate how to apply their MRA framework to meet different risk management needs. The cases focus on prioritizing risk management options, evaluating risk scenarios, and considering health-based targets.

In its *V. parahaemolyticus* MRA, FDA presented the most extensive risk characterization, including a thorough assessment of both uncertainty and variability (U.S. FDA, 2005). The considerable depth and excellent organization of the related appendices are commendable. An additional strength of this MRA is its validation of the MRA output.

5) Risk communication. Three agencies prepared and web-posted interpretative summaries for readers with less of a technical background (U.S. FDA, 2005; USDA, 2005b; WHO, 2005). One had a very brief summary (NZFSA, 2004), and one did not include a summary (WHO, 2006a). Some of the MRAs included extensive, technical appendices (e.g., U.S. FDA, 2005) and some did not (e.g., NZFSA, 2004).

One relevant and outstanding feature of the FDA (2005) MRA, however, was its tiered construction—a summary for general audiences, a report for readers who wish to know more, and the inclusion of numerous appendices that provided detail for the most technically oriented readers. This approach to providing information on differing levels often meets the widest possible range of stakeholder needs. Furthermore, FDA included specific sections describing the criteria and selection procedures for data used in each step of their MRA. The assessment used tables in these sections to highlight the results of the criteria used. An additional feature that strengthened the FDA MRA was the inclusion of specific sections describing assumptions made, and the data sources used in each step of the framework. Overall, the FDA (2005) MRA is highly readable, informative, and innovative in the construction and presentation of its text and graphics.

5.5. KEY ISSUES IN COMPARING MICROBIAL RISK ASSESSMENTS

While the frameworks used in the 13 MRAs were quite similar (some form of problem description preceded the four traditional risk assessment steps), they differed in the implementation and depth of the framework components. Flexibility in applying MRA frameworks is essential for meeting urgent and emerging needs. However, it is striking that no agency to date has conducted and evaluated an MRA using the ILSI (2000) paradigm.[29] In this reviewer's opinion, this framework provides a comprehensive structure and set of individual components that are better suited to MRA than does a modified chemical risk assessment approach. One strength of the ILSI paradigm is its explicit calling out of the many unique factors that influence pathogen-host relationships. Assuring that these and all routes of exposure are considered are important contributions of the ILSI approach.

A recent and key contribution to MRA is the development of a modular approach, particularly to exposure assessments' pathway analyses. The complexity of these pathways can be extraordinary, but the ability to identify self-contained elements that can be modeled effectively is an important

[29] It is noted, however, the two evaluations of the ILSI (1996) paradigm were completed by Teunis and Havelaar and Soller et al., (both in 1999), as bases for the 1999 ILSI workshop that redesigned the original MRA framework.

advancement. In this reviewer's opinion, this approach to implementing MRAs should be more widely applied, and risk assessors should share the lessons learned from using this approach.

Many scientific questions remain to be addressed; all of the MRAs noted research and data needs. Data are insufficient to implement many of the desired MRA models (Yoe, 2003). For example, data are needed on strain virulence factors, dose-response relationships, exposure characteristics, subpopulation characteristics, dynamics of disease spread in populations, animal model extrapolations, and illnesses due to toxins generated by microorganisms (Krewski et al., 2004). While significant data deficiencies exist, MRA methods, pathogen test protocols, and sampling schemes need to be advanced as well (Gardner, 2004).

Currently, the extent of missing or insufficient data is much greater in most MRAs than in chemical risk assessments, resulting in a greater degree of uncertainty. Additionally, the extent to which MRA components vary is largely unknown, making the steps to understand the sources of variability as well as uncertainty in the final modeling results more important. The value of conducting sensitivity and probabilistic analyses to reveal the impacts of variations in MRA components cannot be overestimated. The insights gained will not only be useful for the specific MRA being conducted, but will also contribute to the body of knowledge about microbial pathogens, factors that influence their impacts on human health, and factors that affect MRA methods and results.

Most importantly, understanding the sources of uncertainty and variability remains crucial for ensuring informed decision-making and selection of appropriate risk management options. While methods exist to assess and describe uncertainty and variability impacts on MRA outputs, more needs to be done to enhance comprehension of the rich information embodied in graphic displays of quantitative distributions. Furthermore, the explicit identification of assumptions used in MRA models is essential; en excellent example is demonstrated in the FDA (2005) MRA for raw oysters.

The ability to conduct an effective MRA may be constrained by several factors, including the lack of skilled personnel to fully implement the analytic steps. An incomplete understanding of source-pathway-receptor elements and linkages also limits the conduct of MRAs (Godfrey and Smith, 2005). Important gaps in knowledge about disease processes and microbial pathogen lifecycles require assumptions and uncertainty analysis (Parkin, 2002).

When MRA products are needed in an emergency context, risk managers will find it difficult to implement all MRA framework steps effectively. In anticipation of future needs, organizations may want to consider developing clearer managerial processes to guide MRAs when urgency is a driver.

Identifying the leader to convene the MRA team and the mechanism to clarify the statement of purpose and scope of the MRA are crucial first steps.

6. ENVIRONMENTAL MEDIA AND MICROBIAL RISK ASSESSMENT

The purpose of this section is to comment on issues related to environmental media identified in various MRAs, including those evaluated in section 5. While the focus of the discussion here is on the modules used to organize the MRAs, key media-specific concerns and methods are also presented.

6.1. AIR

There are two general types of exposure models for airborne pathogens: one for person-person transmission and one for aerosol contamination of foods or other items by humans (environment-person contact). Liao et al. (2005) have described indoor air transmission models for three scenarios: a school, a hospital, and commercial airliner. This infectious disease model includes variables such as respiratory rate, air exchange rate, and numbers of infected and susceptible individuals.

In den Aantrekker et al.'s (2003) study of recontamination of foods during factory processing, researchers identified aerosolization of cleaning chemicals as one way in which pathogens could be introduced into foods. They determined that bacterial residues on processing equipment formed a biofilm that could periodically break off and recontaminate food after pathogens in the food had been inactivated in the processing system.

At the time of this review, government-sponsored airborne pathogen models were under development.

6.2. DRINKING WATER

Numerous studies of drinking water exposures to pathogens have been conducted (e.g., Eisenberg et al., 2005; Haas et al., 1993). It is striking that in these studies the modules considered are very similar. The typical sequence of MRA exposure assessment compartments is

- Source of contamination (e.g., household sewage)
- Raw water source (catchment, reservoir, river, well) for the drinking water supply
- Treatment
- Storage and distribution
- Customer's plumbing and point-of-use devices (least often found element)
- Tap water

- Consumption/exposure

While these modules are followed by dose-response assessments, some MRAs address risk on the individual scale while others address the population level. In the latter case, disease transmission models are used and primary (environment-person), secondary (person-person), and tertiary (person-environment-person) transmission may be included (e.g., Eisenberg et al., 2005).

The French MRA of cryptosporidiosis provides a schematic display of their modeling approach (Pouillot et al. 2004). The major modules are

- Emission
- Consumption
- Exposure
- Effect
  - Dose-response
  - Infection-illness

The diagram clearly shows that the outputs from the emission and consumption modules are combined to create the input for the exposure module. The result of this component is then combined with the results of the dose-response model to produce two effects measures: probability of infection and probability of illness.

EPA's cryptosporidium MRA for the LT2 rule economic analysis modeled infectivity, morbidity, and mortality. The MRA included extensive discussions of the dose-response literature and documented a comparative analysis of the literature. The agency laid out its model for estimating individual risk (Exhibit 5.11 in U.S. EPA, 2005b) as follows:

- Pathogen occurrence
- Source water concentration (for both baseline and LT2 reduction options)
- Finished water concentration

- Consumption
- Daily dose
- Daily risk of infection
- Days of exposure
- Annual risk of infection and illness
- Risk distributions

The final step involved a Monte Carlo model to characterize the distribution of individual risks of illness and death and also the population-scale levels of annual illness and death. The assessment extensively discussed the literature on secondary spread and described decisions as to how the data were used for informing the population-scale estimates. The first step of risk characterization was calculating the annual risk of illness, and the second step applied that result and included the impacts of secondary spread to estimate the population level estimate of the risks of illness and death and finally the benefits obtained when the various versions of the proposed rule were modeled (U.S. EPA, 2005b).

WHO's recently completed MRA of cryptosporidium in drinking water does not use a modular approach, but does provide in-depth descriptions of the pathogen and environmental factors that affect its infectivity and transmission to human hosts (WHO, 2006a). The report also covers the difficulties of accurately monitoring the pathogen in drinking water sources and treated water supplies. The hazard identification step in this MRA is quite detailed. Elements considered in this step include

- The pathogen's taxonomic position
- Life cycle
- Related disease
- Prevalence of the pathogen in human excretions
- Routes of transmission (via food and water, human-to-human and animal-to-human)
- Resistance to chemical disinfection processes

- Persistence in the environment
- Impacts of the pathogen's small size (ability to pass through water filtration systems)
- Infectivity of pathogen strains
- Human and livestock sources
- Oocyst shedding amounts
- Immediate infectivity of the oocysts upon excretion

Furthermore, the assessment carefully considers factors that have influenced disease outbreaks and ways to model those factors. Considerable data are used to characterize the health risks. An important contribution of this MRA is its presentation of three case studies, which demonstrate the value of the MRA's methods for different risk management purposes.

Uniquely, this MRA separates exposure and effect assessment into two distinct processes. The level of detail provided in these two steps is important to ensuring a comprehensive approach to the MRA. Key elements addressed in these two steps are

Exposure assessment

- Methods of detecting Cryptosporidium in water for determining
  - Recovery efficiency
  - Viability/infectivity
  - Specificity
- Monitoring (un)treated drinking water (meaning monitoring data for water systems presumed to be treated but in reality with failed or suboptimal treatment processes).
- Cryptosporidium in source water and removal by treatment
  - Assessment of treatment efficacy
  - Post-treatment contamination
- Consumption of drinking water (presenting data from several nations)

Effects assessment

- Host characterization

- Health effects

- Dose-response analysis
  - Human feeding studies
  - Hit theory for infection (beta-Poisson modeling)
  - Pathogen factors (variations in infectivity among isolates)
  - Host factors (immunity and susceptibility to infection)
  - The spectrum of health outcomes from infection to illness

The detailed examination of key factors in the WHO (2006a) MRA demonstrates how different the issues are in MRAs compared to chemical risk assessments and how important it is to identify and characterize these factors sufficiently to improve the utility of the MRA. The major limitation in implementing this level of assessment is the lack of relevant data for many waterborne pathogens and related health outcomes.

6.3. RECREATIONAL WATER

Recreational water includes both flowing and impounded water, including rivers, lakes, ponds, spas, hot tubs, pools, etc. In risk assessments for impounded waters (e.g., van Heerden et al., 2005), exposure assessments include estimating the concentration of the pathogen in the water, treatment efficacy, rate of pool water change, pH level, viability of the organisms recovered, and consumption. Two risk assessments that have investigated swimming in flowing waters used the following exposure assessment modules (Craig et al., 2003; Soller et al., 2003):

- Raw wastewater

- Source water and ambient environmental factors

- Treatment

- Contact/consumption (dermal and ingestion)

Similar to drinking water, the output of this sequence of steps is sometimes linked to disease transmission models to estimate population risks.

Although WHO has developed HACCP approaches to pathogens in drinking water, no complete, government-sponsored MRA of a pathogen in recreational water was found during this project.

6.4. WASTEWATER

Sewage from animal and human sources can be treated and used for a variety of purposes such as toilet flushing; irrigation of crops, parks, sport playing fields, and golf courses; and recharge of ground water supplies. It also is sometimes inadvertently introduced into recreational water supplies.

Several MRAs have modeled the risks associated with "gray water" or water reuse applications (e.g., Westrell et al., 2004; Ottoson and Stenstrom, 2003). In these evaluations, exposure assessment sub-steps have included examinations of

- Source of contamination
- Transport (distance from source to treatment or point of use) and use (application to agricultural land)
- Treatment
- Post-treatment storage
- Distribution and use (holding ponds or tanks, etc.)
- Contact/consumption in treatment plant or public spaces

These modules from source to contact/consumption would not apply to all cases, but can be tailored to the contexts of the scenario of concern.

No government-sponsored MRA for pathogens in wastewater was found during this project.

6.5. FOOD

Foods vary in the degree of handling, processing, storage, preparation, and their significance and use among differing population groups. To reduce the conceptual and computational challenges in assessing pathogen risks related to foods, MRAs typically focus on subsets of foods, such as fresh produce, minimally processed foods, or highly processed foods.

6.5.1. Fresh Foods

Fresh produce such as lettuce, fruits, and peppers have been studied for microbial contamination and related health risks (e.g., Stine et al., 2005; Petterson et al., 2001). Modules used in exposure assessments for produce that receives little or no processing include

- Secondary treatment effluent used for irrigation
- Distribution and use of irrigation water (holding ponds or tanks, on land, in irrigation systems, etc.)
- Pre-harvest contamination of crops
- Harvest
- Post-harvest contamination
- Handling and preparation of produce
- Contact/consumption

No agency-sponsored MRA for fresh food was located during the course of this project.

6.5.2. Processed Foods

Other foods require processing before retail sales, preparation, and consumption. However, the intensity of processing may vary widely, resulting in a need to consider different modules in conducting exposure assessments of processed foods. This section summarizes the modules used to model pathogen risks associated with processed foods. Nine of the 13 agency-sponsored MRAs reviewed addressed pathogens in foods, and thus are discussed in the following section, with more details about modules in Appendix 1.

Foods that require minimal processing before retail sales include unripened cheese made from raw milk (Lindqvist et al., 2002), shellfish (U.S. FDA, 2005; WHO, 2005; FAO/WHO, 2002c), some fishery products (Ross et al., 2000; Lindqvist and Westöö, 2000), whole and pieced poultry (Nauta et al., 2005; NZFSA, 2004; WHO, 2002; FAO/WHO, 2002c; U.S. FDA, 2001), shell eggs (USDA, 2005b; WHO, 2002; USDA, 1998), and beverages (Syposs et al., 2005).

Other food products such as egg products (USDA, 2005b; 1998); wild game products (Coburn et al., 2005); turkey cordon bleu (Bemrah et al., 2002); pig-meat products (Hill et al., 2003); and ready-to-eat meals (USDA, 2005a; U.S. FDA, 2003a; 2004; U.S. FDA/USDA FSIS, 2001) involve more processing steps and therefore more opportunities for contamination (e.g., den Aantrekker et al., 2003).

WHO's guidelines to strengthen prevention and response systems for food safety includes a six-step schematic of the typical food chain (WHO, 2002). The steps shown are: agricultural production and harvesting, storage and transport of raw commodities, processing and manufacture, storage and transport of processed and manufactured products, wholesale and retail distribution, and food service sector. Table 8 provides a summary of the modules found in the peer-reviewed and government literature. Appendix 1 includes additional details.

Table 8. Summary of exposure pathway modules used in processed food MRAs

FOODS	MODULES								
	Source	Harvest	Post-harvest production	Processing	Transport or Distribution	Storage	Retail sale	Consumer preparation	Consumption
Unripened cheese							X	X Storage	X
Shell eggs	X Farm	X Collection	X Pasteurization		X	X		X	X
Egg products				X Break shells and Pasteurization		X		X Storage, preparation and cooking	
Beverages	X Raw water			X Processing, bottling, capping					X
Shellfish		X	X						X
Fish products	X Fishery	X	X			X		X	X
Wild game products	X Live animal	X Slaughter		X	X				
Broiler chickens	X Farm	X Slaughter		X	X	X		X	X
Turkey products	X Farm	X Slaughter							
Pig meat products	X Farm	X Slaughter		X	X	X		X	X
Highly processed foods	X Raw food ingredients		X X		X	X	X	X	X

Some foods were assessed by several organizations. The opportunity to compare approaches for specific foods are food groups was used to look for substep variations. The comparisons made at this level are described below.

6.5.2.1. *Raw Oysters*

The MRAs most recently completed by FDA (2005) and WHO (2005) were conducted to investigate *Vibrio* spp. hazards associated with raw oysters. The modules and components of these two MRAs are shown in Table 9. Both of these MRAs included scoping steps and described pathogen and host characteristics in the hazard identification and hazard characterization steps. Both discussed characteristics of the food matrix (raw oysters) in hazard characterization, and used the beta-Poisson model to determine the dose-response relationship.

Both MRAs used a modular approach in the exposure assessment step. While the first two modules in the MRAs were Harvest and Post-Harvest, FDA named its third module Consumption, while WHO named its third component Public Health. More importantly, the components of the modules are quite similar and in the same sequence, but the outcomes for these two MRAs are different.

Table 9. FDA and WHO raw oyster MRA modules and components

FDA (2005) modules and components	WHO (2005) modules and components
Harvest	*Harvest*
• Water temperature o Relationship between pathogens in oysters and water temperature	• Water temperature o Relationship between pathogens in oysters and water temperature
• Concentration in oysters at time of harvest	• Concentration in oysters at time of harvest o Duration of harvest o Time to refrigeration o Oyster/air temperature
	• Concentration in oysters at time of initial refrigeration o Duration of cool-down
Post-Harvest	*Post-Harvest*
o Duration of harvest o Time to refrigeration o Oyster/air temperature	• Concentration in oysters at time of cool-down o Die-off rate o Duration of storage
• Concentration in oysters at time of initial refrigeration o Duration of cool-down o Growth rate	• Concentrations at time of consumption o Grams per oyster o Number of oysters per serving
• Concentration in oysters at time of refrigeration o Cold storage time o Die-off rate	
• Pathogenic oysters at retail	
Consumption	*Public Health*
• Pathogenic organisms per serving at consumption o Dose response relationship	• Pathogen dose per serving o Dose-response relationship
• Risk of illness (per serving) o Frequency of servings	• Risk of illness (per serving) o Number of servings consumed by the at-risk population
• Risk of illness (per annum)	• Number of illnesses

6.5.2.2. *Shell Eggs and Egg Products*

USDA's most recent MRA examined the risks associated with *S. enteriditis* in shell eggs and egg products (USDA, 2005b). In this MRA, characteristics of salmonella, factors that affect disease transmission, and related illness are described in the hazard identification step. In the exposure assessment section, separate assessments are completed for shell eggs and egg products

using the modular approaches listed below. Hazard characterization includes dose-response assessment and estimation of a range of adverse health outcome measures (illness, hospitalizations, deaths, and sequelae[30]). The MRA ended with a risk characterization with two sections, one for each type of food of concern.

As Table 10 shows, the exposure assessment modules and components for shell eggs and egg products are similar, but they require consideration of different factors and data sources to implement an MRA for each.

Table 10. USDA Exposure assessment modules and components for shell eggs and egg products

Shell eggs	**Egg products**
Farm-to-Table Progression in Exposure Assessment	*Flow of Egg Products in Exposure Assessment*
• Farm o Salmonella in egg at lay	• Breaking o Salmonella in serving before pasteurization
• Storage 1 o Growth in egg prior to processing	
• Pasteurization o Pasteurization factor	• Pasteurization o Pasteurization factor
• Storage 2 o Growth in egg after pasteurization	• Storage and preparation o Growth in serving after pasteurization
• Preparation o Portions per contaminated egg	
• Cooking o Cooking effect o Salmonella at consumption	• Cooking o Cooking effect

6.5.2.3. *Whole Chickens*

The New Zealand Food Safety Authority's most recently sponsored MRA was for salmonella (non-typhoidal) in whole and pieced chicken (NZFSA, 2004). Relevant characteristics of the pathogen, and domestic versus imported chicken supplies were described in the hazard identification step, with health outcomes and dose response presented in hazard characterization. The ensuing exposure assessment had the following components:

[30] Sequelae noted in this MRA included adverse health outcomes with delayed onset after initial infection and/or illness. Sequelae were identified as: reactive arthritis, urethritis, conjunctivitis, entesopathy, myalgia, weight loss of over 5 kg, dactylitis, erythema nodosum, oral ulcers, myocarditis, acute anterior uveitis, iritis, cholecystitis, keratitis, pharyngitis, and pneumonia.

- Hazard in the New Zealand food supply
  - Salmonella in poultry meat during production and after chilling
  - Salmonella in poultry meat at retail
  - Salmonella prevalence based on a 2003–2004 New Zealand-specific survey

- Food consumption

- Qualitative estimation of exposure
  - Number of servings and serving sizes
  - Frequency of contamination
  - Predicted contamination at retail
  - Growth rate during storage and probable storage time
  - Heat treatment
  - Exposure summary

- Overseas context
  - Salmonella in poultry meat, raw and ready-to-eat

Although not as extensively detailed as Nauta et al. (2005), NZFSA provides sufficient detail for the reader to understand the factors that influence the level of contamination in whole and pieced chicken.

Nauta et al. (2005), however, provided extensive documentation and data for the farm-to-fork pathway for broiler chickens. This MRA's model relied on the Modular Process Risk Model, which includes several stages:

- Farm
- Processing
- Cutting
- Storage
- Consumer preparation
- Ingestion/dose-response

The model also considers multiple opportunities for cross-contamination and removal. The MRA provides graphic representations of the model, detailed equations, and clearly stated

assumptions throughout. It also thoroughly examines the potential impacts of uncertainties and variabilities.

6.5.2.4. *Variety of Foods*

Five MRAs assessed pathogen risks associated with groups of foods:

- Lindqvist and Westöö, 2000: Several types of cold- and hot-smoked fish
- Hill et al. 2003: Three categories of pig-meat products
- Coburn et al., 2005: Food types of processed wild game
- Nauta et al., 2005: Broiler and other meats
- EFSA, 2006c: Foods and beverages

The least detailed qualitative MRA (Coburn et al., 2005) identified the three microbial pathogens that posed the greatest health risks and in which foods.

Lindqvist and Westöö (2000) presented a schematic diagram of their model structure, clearly indicating how each component relates to other parts of the MRA. The primary compartments of the model are

- Concentration of the pathogen in fish
- Number of pathogens consumed
- Dose-response
- Probability of illness (per serving and per year)
- Number of cases per year in Sweden

The authors also provided data and Excel spreadsheets they used in the model, and they presented and discussed results from using two different dose-response models.

Hill et al. (2003) provided extensive detail of their pig-meat products model, with the following major modules:

- Farm
- Transport and lairage
- Slaughter and processing
- Distribution and storage
- Preparation and consumption
- Human effect

The detailed report of this MRA provides a purpose statement for each module, the data and equations used, modeling decisions, assumptions, and assessments of the impacts of uncertainties and variabilities. Several scenarios are used to assess the impacts of specific parameters. Limitations of the modeling approach and results are included. The model also considers multiple opportunities for cross-contamination and removal. The MRA provides graphic representations of the model, detailed equations, and clearly stated assumptions are provided throughout. The potential effects of uncertainties and variabilities are thoroughly examined.

EFSA (2006c) provided detailed toxicological data for the renal, nervous, immune, and reproductive systems in addition to cancer. The authors also presented consumption data derived from three European nations.

The modular approach used by Nauta et al (2005) is described in section 6.5.2.3.

6.6. BIOSOLIDS

A few risk assessments have been completed for biosolids—animal waste on pastures used for recreation, and biosolids used on agricultural lands (Eisenberg et al., 2004; Gerba et al., 2002; Strachan et al., 2002).

In these cases, the modelers used the following modules in their exposure assessments:

- Pathogen sources and intermediate hosts
- Pathogen fate and transport in the environment
- Pathogen resistance to environmental conditions

- Pathogen occurrence in biosolids
- Pathogen survival of biosolid treatment processes
- Use of biosolids (land applications)
- Environment-person contact/exposure

When secondary and tertiary transmission and population risk estimates are needed, the exposure assessment outcomes have been linked to disease-transmission models.

Eisenberg et al. (2006) have proposed a dynamic modeling approach to estimating human health risks due to biosolid uses. Exposure scenarios and exposure pathway models (groundwater and aerosol) provide the statistical inputs for estimating three risk measures: individual single event level risk, annual individual level risk, and population level attributable risk. Based on the first ILSI framework (ILSI, 1996), five components—wastewater, wastewater treatment, sludge treatment, biosolids application, and exposure—represent the environmental processes that lead to human exposures. The health effects part of the framework includes modeling health effects (using either static or dynamic models) and characterizing risk.

No agency-sponsored MRA of biosolids was found at the time of this review.

6.7. GENETICALLY MODIFIED ORGANISMS

The MRA of *Streptomyces lydicus* WYEC 108 (U.S. EPA, 2004a) reviewed in this project is an example from a series of assessments conducted on modified organisms used in food processing and other purposes. The emphasis in these evaluations is on toxicological evidence, because these organisms are not approved for use at the time of assessment. Exposure potentials for various routes and populations (e.g., occupational and susceptible groups) are considered but no pathway analyses are conducted. Risk characterizations are brief, but margins of exposure and uncertainty factors may be applied to protect vulnerable populations.

The recent publication of guidelines related to genetically modified organisms (e.g., EFSA, 2006a; FAO/WHO, 2003b), however, suggests that MRAs for these organisms may be in process and published in the near future.

6.8. INTENTIONAL USES OF MICROBES

The U.S. Centers for Disease Control and Prevention (CDC) has selected and prioritized biological terrorism agents using a qualitative risk assessment approach (CDC, 2002). Based on judgments of each agent's potential public health impacts, potential for widespread distribution among populations, public perception of each agent, and specific public health preparedness needs, CDC categorized pathogens into three classes (A, B, and C) to guide preparedness planning.

6.8.1. Contamination

Two estimates of human exposure and related health risks have been completed for the 2001 postal anthrax event (Fennelly et al., 2004; Webb and Blaser, 2002). While neither study used a risk assessment framework, both used mathematical models to obtain exposure and risk estimates. Webb and Blaser simulated a series of cross-contaminations of mail using a matrix model, while Fennelly et al. used the Wells-Rilely model (as in Liao et al., 2005) to estimate ambient exposures to anthrax spores and risk of infection. Components of these models included both environmental and host factors, such as room air exchange rates, pulmonary ventilation rates, age, duration of exposure, etc.

At the time of this review, contamination models were under development.

6.8.2. Clean-Up

EPA's National Homeland Security Research Center has described an incident-response MRA framework (Nichols et al., 2006). The exposure assessment step requires data on the type of microorganism, number and locations of release points, time and duration of releases, area of contamination, population exposed, population behaviors, exposure scenarios, and other factors. The outcomes of this assessment are prediction of the area of contamination, potentially exposed population, potential exposure point concentrations, and exposure intakes. Presumably, these outcomes would be used to assist in clean-up decision-making.

At the time of this review, clean-up models were under development.

6.9. KEY ISSUES RELATED TO ENVIRONMENTAL MEDIA

Media-specific factors and characteristics are important to pathogen survival, persistence, growth, and die-off. The significance of having a comprehensive organizational structure and components to characterize the pathogen's progress from source to host cannot be

overemphasized. Each environmental medium or matrix entails different challenges and opportunities for pathogens. It is easy to miss crucial factors in such complex conditions without the benefit of a conceptual model and systematic framework to guide the assessors' consideration of the many factors and their inter-relationships. These pathways are complex, requiring detailed compilations of concepts and data to adequately inform and conduct MRAs. Furthermore, translation of the factors and relationships into tractable formulas requires additional technical skill and attention to detail.

Developing broad, flexible categories of MRA elements is an important goal in module development. Modules should not be rigid lists of steps or elements to consider in every MRA, but rather groupings of characteristics to be considered in specific risk assessments. Like frameworks, modules could serve as guides, not cookbooks, for risk assessors. Particularly in the context of urgent political and/or public health scenarios, modules can help assure that complete and effective MRAs are implemented.

Modules produce more transparent organization and greater description of the many factors that contribute to pathogen-related health risks. Modules could be constructed to assure that they align with functional components of the pathogen's pathway and facilitate the design and conduct of mathematical models for essential inputs to the successive module and MRA steps.

7. RECOMMENDATIONS

Although similarities exist among many microbial risk assessment frameworks, the differences may result in important variations in MRA results. Beginning with effective planning and scoping, problem formulation, definitions and a sound conceptual model are essential to conducting a meaningful and relevant MRA. Getting the questions right early in the process through dialogue with risk managers is a crucial step. Developing a sound and comprehensive conceptual model may require several iterations, but it is suggested that identifying the fundamental components of the model be done early, so the model will focus on risk managers' needs.

One way to develop an effective set of risk questions and a conceptual model is to use systems thinking or concept-mapping approaches, as described in section 5.1 (e.g., Trochim et al., 2006). These methods can help set the boundaries of the MRA problem statement and scope, reveal valuable insights about the problem and MRA process, and facilitate more comprehensive and precise thinking about MRA issues.

Furthermore, agencies responsible for specific types of MRAs (e.g., food, water) may be able to identify modules that they will commonly need for the MRAs within their authorities. A large number of the elements required for each module could be listed and organized in advance, and the elements could be further refined when specific applications are defined. These modules could be drafted within agencies and vetted among panels of peer reviewers to provide organizations with rapidly accessible, off-the-shelf components for MRAs.

Assessors are encouraged to continue working toward more reader-friendly ways of presenting their modeling activities and results. The FDA (2005) MRA includes a number of innovations that may be suitable for other MRAs. Improved communication strategies for a wide range of stakeholders may yield important partnerships that could enable improvements in MRA data sources and approaches.

Few validations of MRAs have been completed to date. It is often difficult to locate enough data to both run the models and to set aside enough data to use for later validation. When more data become available to evaluate the models, MRAs can then be revised and improved. There are many needs for new research and technologies to improve MRA precision and accuracy. Data are needed to more fully populate components of MRA paradigms; such research will take time and resources.

With comprehensive paradigms to help risk assessors identify and consider the many potential factors involved in pathogen-related illness, MRAs will become increasingly

informative and contribute to more effective public health interventions. Risk assessors are encouraged to share the lessons they learn in conducting MRAs and to continue developing effective, strategic approaches to MRA models and communications.

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APPENDIX 1. PROCESSED FOOD MODULES

The purpose of this appendix is to provide more specific information about exposure pathways modules for the MRAs summarized in section 6 and Table 8. See additional citations in section 6.

Unripened cheese.

The modules used to assess contamination in the unripened cheese were for microbial levels at the time of retail sale, storage, and consumption.

Shellfish.

For shellfish MRAs, exposure assessment modules included

- Harvest
- Post-harvest
- Public health (epidemiology and consumption)
- Consumption

Shell eggs.

Exposure assessments of shell eggs have included modules such as

- Production
- Processing, distribution, and storage
- Preparation and consumption

Egg products.

For egg products, the processing step has been modified to consider the additional conditions involved in breaking the shell and using the egg to create egg products.

Beverages.

In a beverage risk assessment, the modules used were

- Raw water
- Water treatment
- Use of water in production, additional processing, bottling, and capping

Fish products.

Modules used for fishery products included

- Fishery ecology
- Fish microbial growth factors
- Lag times and death rates
- Thermal inactivation (cooking)
- Non-thermal inactivation
- Serving
- Consumption

The Swedish framework used to guide the implementation of the four-stage model involved a series of mathematical models (Figure 1 in Lindqvist and Westöö, 2000). Each model generated a quantitative output that became the input for the next model in the series. The concentration of *L. monocytogenes* in a fish and serving size data were combined to obtain the total number of microorganisms consumed (exposure). Combined with dose-response data in two models (hazard characterization), this outcome was used for the risk characterization step (e.g., to estimate the probability of illness per serving and per year at the individual level, including among susceptible subpopulations). The number of listeriosis cases per year in the country was estimated by considering the amount of contaminated food consumed per year and the number of exposures per year in Sweden. Throughout the risk assessment, assumptions were clearly noted, and their potential impacts on the final estimates were analyzed and discussed along with recommendations for risk reduction strategies. Data gaps were mentioned as well (Lindqvist and Westöö, 2000).

Broiler chickens.

For broiler chickens, risk assessment modules have included

- Farm and transport
- Slaughter and processing
- Transport and processing
- Retail distribution and storage

- Preparation
- Consumption

The preparation component considered cross-contamination and undercooking in domestic food settings.

Wild game.

Four types of processed wild game were examined: gamebirds, wild ducks, wild deer, and wild lagomorphs (Coburn et al., 2005). The risks due to eight microbial pathogens and lead shot were estimated qualitatively. The human exposure pathway (see Figure 1 in Coburn et al., 2005) was laid out in four major steps:

- Live wild animal
- Transport and processing
- Storage, distribution and retail
- Preparation and consumption

At each step health risks associated with handling were considered. The risk of illness associated with consumption was evaluated in the final step.

Pig-meat products.

Hill et al. (2003) used a framework to guide this assessment, which was a "farm to consumption" approach, involving five modules:

- Farm (prevalence)
- Transport and holding (prevalence)
- Slaughter and processing (prevalence and concentration)
- Distribution and storage (prevalence and concentration)
- Preparation and consumption (prevalence and concentration)
- Health effects

Three sets of pig-meat products were examined: pork, mixed meat products, and bacon. Both fresh and chilled products, which were cooked improperly or cross-contaminated other foods, were considered.

Within each module, a mathematical model of biological processes was implemented to characterize their impacts on pathogen prevalence and, in some cases, concentrations. Parameters in the farm module were varied to evaluate the impacts of various possible pathogen-control methods. The output of the preparation and consumption module was the probability of a person ingesting the pathogen and the number of organisms consumed. These results became the inputs for the human effects (dose-response) module.

The report presents extensive descriptions of each module, with equations and assumptions (Hill et al., 2003). Data gaps are noted for each component, as appropriate to the state of the science at the time the module was implemented. Tables and figures showing the results for the scenarios are presented and compared to baseline conditions. These presentations and the authors' discussions offer decision-makers valuable information for understanding and interpreting the data as they choose among control options.

Highly processed foods.

The modules used for more highly processed foods (e.g., turkey products, ready-to-eat foods and meals) were

- Raw food ingredients
- Live bird contamination
- Slaughter and processing
- Food product processing (mincing of meat, reconstituting or mixing raw ingredients)
- Transport and storage
- Contamination at the point of retail sale
- Microbial growth between sale and consumption
- Storage, preparation, and cooking
- Consumption

Variety of routes of exposure.

In The Netherlands' risk assessment of campylobacter, various routes of exposure (broiler and other meats, contact with pet and farm animals, and consumption of raw and undercooked foods) were examined to determine which route/s had the most significant impacts on public health (Nauta et al., 2005). The transmission and concentrations of campylobacter in the broiler meat part of the MRA were modeled within modules in the "farm to fork" chain to obtain "units" of potentially contaminated food or animal items (e.g., on the exterior of a carcass or filet). The modules were designed to characterize the impacts of: bacterial processes such as

growth and inactivation, food handling processes including partitioning, mixing, cross-contamination, and finally, removal.

In each module, the dynamic factors and often non-linear processes that affected pathogen concentrations were modeled using Monte Carlo methods. Each model produced an output that was used as the input for the next model in the pathway. The report acknowledged sources of variability and uncertainty and assumptions used to design and implement the model. One important limitation was the lack of information for constructing model parameters and relationships among them.