Food and Agriculture Organization of the United Nations

World Health Organization

Joint FAO/WHO Expert Meetings on Microbiological Risk Assessment (JEMRA) on Methodologies of Microbiological Risk Assessment

Draft Guidance of Microbiological Risk Assessment for Food

Public consultation

Posted on 15 June 2020

Background information

Risk assessment of microbiological hazards in foods, commonly referred to as Microbiological Risk Assessment (MRA), has previously been identified as one of the priority areas of work by the Codex Alimentarius Commission (CAC). Following the work of the Codex Committee on Food Hygiene (CCFH), CAC adopted Principles and Guidelines for the Conduct of Microbiological Risk Assessment (CXG-30) in 1999.

Subsequently, the CCFH identified a number of areas in which it required expert risk assessment advice.

In response to the needs of their member countries and Codex, FAO and WHO launched a programme of work in the early 2000's with the objective of providing expert advice on risk assessment of microbiological hazards in foods, including technical guidance on microbiological risk assessment. Three technical guidance documents were published in the Microbiological Risk Assessment Series: Hazard characterization for Pathogens in food and water (2003), Exposure assessment of microbiological hazards in food (2008), and Risk characterization of microbiological hazards in food (2009).

Science has evolved over the last decade and there is a need to update and incorporate new developments in the principles and methods for risk assessment of microbiological hazards.

To consolidate and update the existing technical guidance documents on microbiological risk assessment, FAO and WHO established a group of experts and convened the Expert Meetings in Rome, Italy on 11-15 March 2019. In addition, the draft document was also subject to peer review by external reviewers.

Comments

If you have any comments, please contact us at both jemra@fao.org and jemra@who.int no later than **15 July 2020**. When you provide us your comments, please indicate line number (left) for specific chapters/sections.

(DRAFT) Guidance of Microbiological Risk Assessment for Food

Joint FAO/WHO Expert Meetings on Microbiological Risk Assessment (JEMRA) on Methodologies of Microbiological Risk Assessment

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Glossary

Baseline risk (Inherent risk): The level of food safety risk posed by a hazard in a food supply chain without any changes to the current system, i.e. without additional risk management options being implemented.

Dose-Response Assessment: The determination of the relationship between the magnitude of exposure (dose) to a chemical, biological or physical agent and the severity and/or frequency of associated adverse health effects (response). (CAC, 2019)

Exposure Assessment: The qualitative and/or quantitative evaluation of the likely intake of biological, chemical, and physical agents via food as well as exposures from other sources if relevant. (CAC, 2019)

Hazard: a biological, chemical or physical agent in, or condition of, food with the potential to cause an adverse health effect. (CAC, 2019)

Hazard Characterization: The qualitative and/or quantitative evaluation of the nature of the adverse health effects associated with biological, chemical and physical agents which may be present in food. (CAC, 2019)

Hazard Identification: The identification of biological, chemical, and physical agents capable of causing adverse health effects and which may be present in a particular food or group of foods. (CAC, 2019)

Qualitative Risk Assessment: A risk assessment based on data which, while forming an inadequate basis for numerical risk estimations, nonetheless, when conditioned by prior expert knowledge and identification of attendant uncertainties permits risk ranking or separation into descriptive categories of risk. (CAC, 1999)

Quantitative risk assessment: A risk assessment that provides numerical expressions of risk and indication of the attendant uncertainties. (CAC, 1999)

Ranking: The process of ranking different hazard-food product combinations for risk assessment and/or risk management priority.

Risk: A function of the probability of an adverse health effect and the severity of that effect, consequential to a hazard(s) in food. (CAC, 2019)

Risk Analysis: A process consisting of three components: risk assessment, risk management and risk communication. (CAC, 2019)

Risk Assessment: A scientifically based process consisting of the following steps: (i) hazard identification, (ii) hazard characterization, (iii) exposure assessment, and (iv) risk characterization. (CAC, 2019)

Risk Characterization: The process of determining the qualitative and/or quantitative estimation, including attendant uncertainties, of the probability of occurrence and severity of known or potential adverse health effects in a given population based on hazard identification, hazard characterization and exposure assessment. (CAC, 2019)

Risk Communication: The interactive exchange of information and opinions throughout the risk analysis process concerning risks, risk-related factors and risk perceptions, among risk assessors, risk managers, consumers, industry, the academic community and other interested parties, including the explanation of risk assessment findings and the basis of risk management decisions. (CAC, 2019)

Risk estimate: The qualitative and/or quantitative estimation of risk resulting from risk characterization. (CAC, 2019)

Risk Management: The process, distinct from risk assessment, of weighing policy alternatives, in consultation with all interested parties, considering risk assessment and other factors relevant for the health protection of consumers and for the promotion of fair trade practices, and, if needed, selecting appropriate prevention and control options. (CAC, 2019)

Risk profile: The description of the food safety problem and its context. (CAC, 2019)

Semi-quantitative risk assessment: Semi-quantitative risk assessment involves assigning numbers to qualitative estimates of exposure and the dose-response relationship, in the form of probability ranges, weights or scores, and combining them by addition, multiplication, or other mathematical operation, to arrive at a risk estimate with the objective of achieving a greater level of objectivity compared to a qualitative risk assessment approach.

Sensitivity analysis: A method used to examine the behaviour of a model by measuring the variation in its outputs resulting from changes to its inputs. (CAC, 1999)

Transparent: Characteristics of a process where the rationale, the logic of development, constraints, assumptions, value judgements, decisions, limitations and uncertainties of the expressed determination are fully and systematically stated, documented, and accessible for review. (CAC, 1999)

Uncertainty analysis: A method used to estimate the uncertainty associated with model inputs, assumptions and structure/form. (CAC, 1999)

1. Introduction

1.1 FAO/WHO Series of Guidelines on Microbiological Risk Assessment

The General Agreement on Tariffs and Trade (GATT), was established under the United Nations in 1947 as a series of international meetings at which nations would work together to reduce tariffs and other barriers to eliminate unfair and discriminatory practices in international commerce. In relation to food, the overarching principle was that, for nations to develop, export income from agricultural products was the first step in the economic development of those nations. Completion of the eighth, or 'Uruguay round', of GATT negotiations, in 1994, led to the creation of the World Trade Organization (WTO).

Importantly, the rules and disciplines of the WTO Agreements – the Sanitary and Phytosanitary (SPS) and the Technical Barriers to Trade (TBT) Agreements – are designed to minimise the negative effect on trade of food safety regulations that cannot objectively be justified. What this means is that scientific data and arguments and conclusions based on them, i.e. 'science-based' arguments, are the only basis for restrictions to international trade in foods.

The WTO recommendations specified the need for science-based food safety regulations but, when those rules were introduced, there were no established, internationally accepted, procedures for science-based assessment of microbiological food safety risk. The development of science-based standards was considered the role of Codex. Accordingly, FAO and WHO established the Joint Expert Meetings on Microbiological Risk Assessment (JEMRA[1]) – similar to the already well-established Joint FAO/WHO Expert Committee on Food Additives (JECFA[2]) – to develop the methods and the tools needed to facilitate the WTO ambitions. As part of that process Codex also developed a set of principles and guidelines for the conduct of microbiological food safety risk assessment (CAC, 1999).

In response to the needs of their member countries and Codex, FAO and WHO, through JEMRA, launched a programme of work in the early 2000's with the objective of providing expert advice on risk assessment of microbiological hazards in foods. FAO and WHO undertook development of guideline documents for the hazard characterization (FAO/WHO, 2003), exposure assessment (FAO/WHO, 2008), and risk characterization (FAO/WHO, 2009a) steps of risk assessment. The need for such guidelines was highlighted in the work being undertaken by FAO and WHO on risk assessment of specific commodity-hazard combinations and it was recognized that reliable and consistent estimates of risk in the risk characterization step were critical to risk assessment.

Over the years, since the guidelines were first developed, much experience has been gained in risk assessment. By 2017, FAO and WHO recognized that a single, updated document on risk assessment was needed, including additional guidance on hazard identification. To this end, this FAO/WHO guideline is intended to provide practical guidance and a structured framework for carrying out each of the four components of a microbiological risk assessment described below, whether as part of a full risk assessment, as an accompaniment of other evaluations, or as a stand-alone process.

These guidelines are not intended to be prescriptive, nor do they identify pre-selected compelling options. They provide descriptive guidance on how to conduct a risk assessment, utilizing a variety of tools and techniques. They have been developed in recognition of the fact that reliable estimation of risk combined with appropriate uncertainty analysis is critical for transparent and consistent risk

[1] http://www.fao.org/food/food-safety-quality/scientific-advice/jemra/en/ accessed 6 August 2019
[2] http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/en/ accessed 6 August 2019

management decision making as well as for effective risk communication within the risk analysis framework.

1.2 Scope and Purpose of these guidelines

This document provides guidance on undertaking risk assessment of all microbial hazards which may adversely affect human health in foods along the food supply chain; included are microbial toxins that result in acute illness and where the dose of the microbial toxin is stoichiometrically related to the level of contamination of the toxigenic organism in the food. This document is also intended to provide practical guidance on a structured framework for carrying out risk assessment of microbiological hazards in foods, focusing on the four components including hazard identification, hazard characterization, exposure assessment and risk characterization. These guidelines therefore represent the best practice at the time of their preparation, and it is hoped that they will help stimulate further developments and disseminate the current knowledge.

The overarching objectives of these guidelines are to help the reader to:

- identify the key issues and features of a microbiological risk;
- recognize the properties of a best-practice risk assessment;
- avoid some common pitfalls of risk assessment; and
- perform risk assessments that are responsive to the needs of risk managers.

1.3 Guiding the reader through this document

The primary audience for this MRA guideline is the global community of scientists and risk assessors, both experienced and inexperienced, in risk assessment, and the risk managers or others responsible for risk decision making and/or communication.

Ideally, the reader would begin with the Report of a Joint FAO/WHO Consultation entitled Principles and guidelines for incorporating microbiological risk assessment in the development of food safety standards, guidelines and related texts (FAO/WHO, 2002a). That report appropriately establishes the purpose of risk assessment as meeting the needs of risk managers. With that report as background the reader would ideally read the current guidelines for risk assessment next.

On some issues, an approach is advocated based on a consensus view of experts to provide guidance on the current science in risk assessment. On other issues, the available options are compared and the decision on the approach appropriate to the situation is left to the analyst. In both of these situations, transparency requires that the approach and the supporting rationale be documented.

1.4 How to begin with risk assessment

Microbial risk assessment can often seem overwhelming to those faced with the task of developing a risk assessment for the first time. There are several books that can be helpful for the beginner or the advanced beginner. Training courses are also available from recognized experts in the field. Finally, and perhaps of greatest value, is to work with an experienced practitioner over an extended period to develop a risk assessment. The list of books and training providers below are not meant to be all-inclusive, nor do they imply endorsement, but they represent a good starting place.

Books

- Haas, Charles N., Joan B. Rose, and Charles P. Gerba. Quantitative Microbial Risk Assessment. 2nd Ed. John Wiley & Sons, 2014.
- Schaffner, Donald W (editor). Microbial Risk Analysis of Foods. ASM Press, 2008.
- Vose, David. Risk analysis: A Quantitative Guide. John Wiley & Sons, 2008.

- WHO/FAO. Food safety risk analysis: A guide for national food safety authorities, 2007.

Training

- Center for Advancing Microbial Risk Assessment http://camra.msu.edu/
- Epiχ Analytics https://www.epixanalytics.com/
- FAO/WHO/ICD basic awareness course on Microbiological risk assessment available at: http://www.fao.org/waicent/faoinfo/food-safety-quality/mra/mra_en/index.html
- Joint Institute for Food Safety and Applied Nutrition https://jifsan.umd.edu/training/risk/registration/catalog
- Risk Sciences International, Inc. https://www.risksciences.com/course/quantitative-food-safety-risk-assessment/

Part 1 General Considerations

2. Risk Assessment in Context

2.1 Risk Analysis Framework

Risk analysis is defined by Codex Alimentarius Commission (CAC) as "a process consisting of three components: risk assessment, risk management and risk communication" (CAC, 2018), with the three components defined as follows:

- Risk Assessment – A scientifically based process consisting of the following steps: (i) hazard identification, (ii) hazard characterization, (iii) exposure assessment, and, (iv) risk characterization
- Risk Management – The process, distinct from risk assessment, of weighing policy alternatives, in consultation with all interested parties, considering risk assessment and other factors relevant for the health protection of consumers and for the promotion of fair-trade practices, and, if needed, selecting appropriate prevention and control options.
- Risk Communication – The interactive exchange of information and opinions throughout the risk analysis process concerning risk, risk-related factors and risk perceptions, among risk assessors, risk managers, consumers, industry, the academic community and other interested parties, including the explanation of risk assessment findings and the basis of risk management decisions.

Risk analysis is used to develop an estimate of the risks to human health, to identify and implement appropriate measures to control the risks, and to communicate with stakeholders about the risks and measures applied. It can be used to support and improve the development of standards, as well as to address food safety issues that result from emerging hazards or breakdowns in food control systems. It provides risk managers with the information and evidence they need for effective decision-making, contributing to better food safety outcomes and improvements in public health. Regardless of the institutional context, the discipline of risk analysis offers a tool that all food safety authorities can use to improve food safety.

2.2 Risk Management

A generic process for carrying out risk management is presented in Figure 1. Such frameworks developed at the international level provide useful templates for countries developing their own risk management systems. In addition, the CAC has developed principles and guidelines for the conduct of microbiological risk management (CAC, 2008).

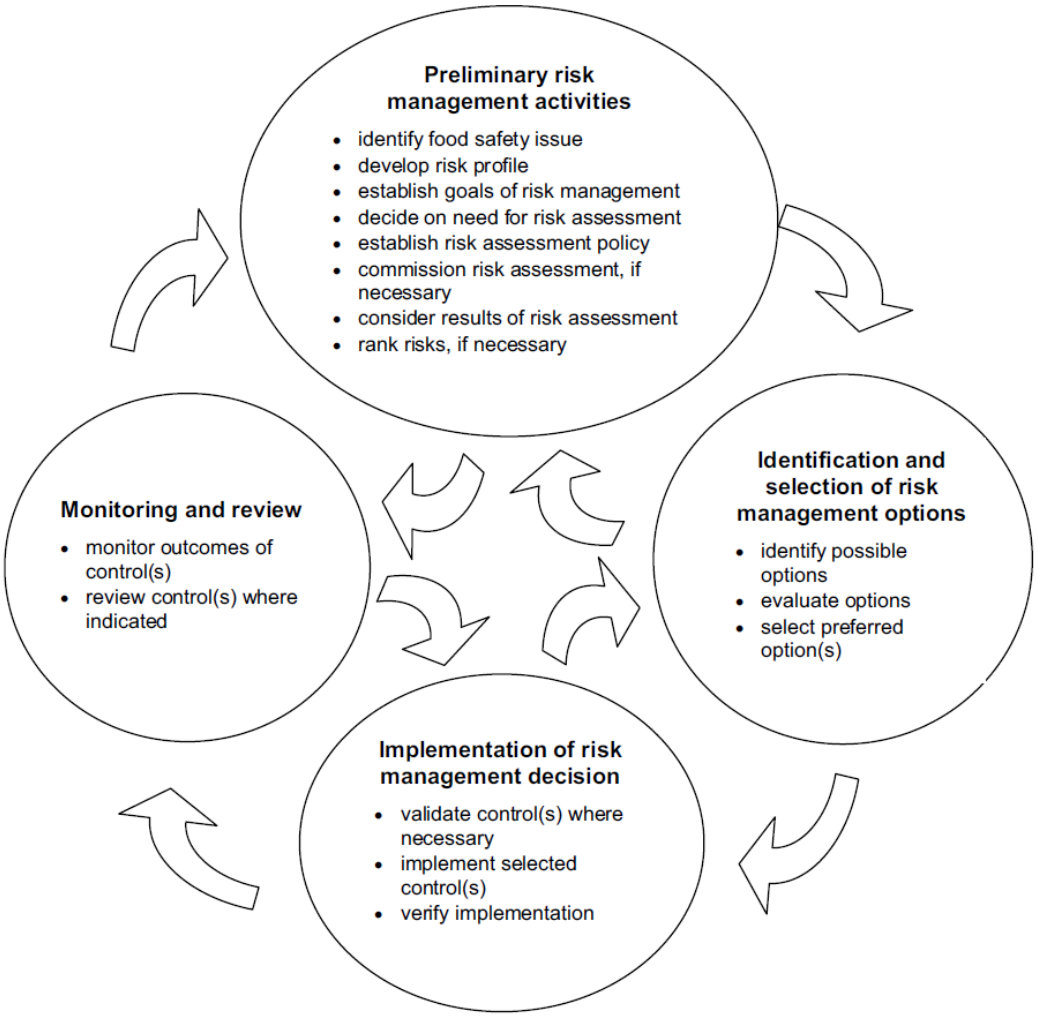


Figure 1: Generic Risk Management Framework (RMF) as presented by FAO/WHO (2006, Figure 2.1)

The first phase of the Risk Management Framework (RMF) shown in Figure 1 consists of "preliminary risk management activities". After a food safety issue has been identified, available scientific information is aggregated into a risk profile that will guide further action.

The second phase of the RMF consists of identifying and evaluating a variety of possible options for managing (e.g. controlling, preventing, reducing, eliminating or in some other manner mitigating) the risk.

The third phase of the RMF refers to the implementation of the selected risk management options by the relevant stakeholders. In many countries, industry has the primary responsibility for implementing regulatory standards or other food safety measures under government or customer oversight. National food safety authorities, or certified 'third party' auditors, must verify implementation of regulatory standards and verify the implementation and effectiveness food safety programs, such as HACCP. In addition, some risk management options may be adopted, such as quality assurance schemes at the farm level, or consumer education packages for food handling in the home that can also contribute to risk reduction. Guidelines on the translation of microbial food safety risk assessment into risk management actions are presented in FAO/WHO (2006b).

Once control measures have been implemented, monitoring and review activities should be carried out (the fourth phase of the RMF). The goal is to determine whether the measures that were

selected and implemented are, in fact, achieving the risk management goals they were meant to achieve, and also whether they are having any other *unintended* effects. Both industry and government bodies are likely to be involved in monitoring and review activities. Both sectors usually monitor levels of hazard control, while government generally carries out surveillance of the level of food-borne illness in the population. If monitoring information indicates a need to review the risk management options, the risk management process can begin a new cycle, with all interested parties participating as appropriate.

When dealing with a given specific food safety issue, the RMF can be entered at any phase and the cyclical process can be repeated as many times as is necessary. Further details can be found in the food safety risk analysis guide published by WHO/FAO (2006).

2.3 Risk Assessment

Risk assessment is a 'decision support' tool. Its purpose is not necessarily to further extend scientific knowledge but to provide risk managers with a rational and objective picture of what is known, or believed to be known, about health risk and its causes at a particular point in time. It is the risk manager's responsibility to consider the risks alongside other decision criteria (sometimes referred to in WTO as "other legitimate factors"), such as nutrition, food security, social & cultural aspects, technical feasibility, cost-vs-benefit, and environmental and economic aspects (FAO, 2017). Nevertheless, risk assessment may also involve judgments and choices that are not entirely scientific, and risk managers need a sound understanding of scientific approaches and assumptions used by risk assessors.

In several frameworks, risk assessment is broken down into a number of stages but, in general, risk assessment is the 'umbrella' term used to describe the complete process of assessing a risk. The Codex guideline CAC/GL-30 (CAC, 1999) defined risk assessment for microbiological hazards in foods as a scientifically based process comprising four components (Figure 2), which are described below and systematically addressed in the various parts of this guidance document. For all components, the sources and magnitude of variability and uncertainty (see Chapter 14) should be described, although the extent to which this can be done will depend on the data available and the risk assessment approach being taken.

- **Hazard Identification** (Chapter 4) is a qualitative process intended to identify microbial hazards of concern in food. Microbial hazards can include infectious agents or toxins produced by microorganisms. For well-documented microbiological hazards, this step is straightforward while more work will be required if the hazard is new or emerging. If a comprehensive risk profile has already been developed, then this step may be very simple. During hazard identification, the associations between microbiological hazards and specific food commodities and certain high-risk groups in the population should be identified.
- **Exposure Assessment** (Chapter 5) is the qualitative and/or quantitative evaluation of the likely intake of a microbial hazard via specific foods with the potential to cause an adverse health effect. It should provide a qualitative and/or quantitative estimate of the likelihood and level of the hazard in a specified consumer portion of that food or a specified volume of water, taking into account all pertinent parts of the food chain and pathways. The exposure assessment may also identify the frequency and amount of food and water consumed in a given period for a given (sub-) population and may combine the information to estimate the population exposure to a microbiological hazard. Often the exposure assessment will detail the various steps of the farm-to-fork pathway so that the influence of individual

steps/processes, or changes to them, can be assessed. This is often very powerful information for assessing risk management options.

- **Hazard Characterization** (Chapter 6) provides a description of the adverse effects that may result from ingestion of a hazard, whether that is a microorganism or its toxin, and articulation of a dose-response relationship where possible. Those health effects include, for example, diarrhoeal illnesses, hospitalizations and deaths, and in the context of MRA are usually considered to be acute, rather than chronic illnesses. This component may include identification of different adverse effects, including sequalae and their likelihood, for different subpopulations, such as neonates or immunocompromised people.
- **Risk Characterization** (Chapter 7) is the integration of the three previous steps to derive a risk estimate, i.e. an estimate of the likelihood and severity of the adverse effects that occur in a given (sub-)population, with associated uncertainties from consumption of a food contaminated with the hazard. It is in the risk characterization step that the results of the risk assessment are presented. These results are provided in the form of risk estimates and/or risk descriptions that provide answers to the questions that the risk managers posed to the risk assessors. These answers, in turn provide the best available science-based evidence to be used by risk managers to assist them in managing food safety risks.

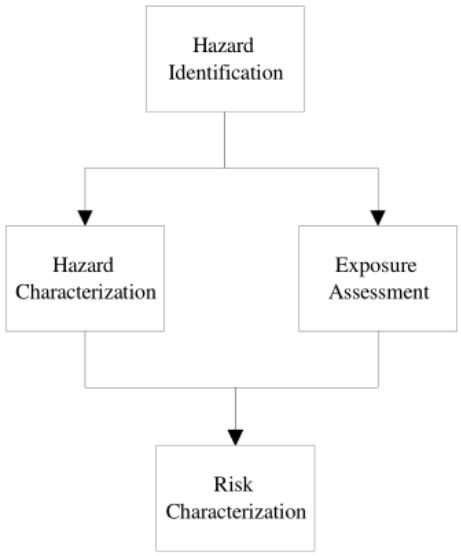


Figure 2: Components of a Risk Assessment

The World Organisation for Animal Health (OIE) has also defined the risk assessment (OIE, 2018). However, as the OIE guidelines focus on risk assessment from the perspective of import and export of aquatic and terrestrial animals the steps are slightly different.

2.4 Risk Communication

The ultimate objective of risk communication is to inform and enhance risk assessment and risk management strategies, inform people who may be involved in risk mitigation, i.e. implementing chosen risk management options, and to enable people who are exposed to the risk to be involved in how they protect their own and others' health from the food safety risk. Risk communication is an integral and ongoing part of the risk analysis process and, ideally, all stakeholder groups should be involved from the start. This means that risk communication is a two-way process which involves understanding and consideration of all stakeholder feedback, perceptions and willingness to accept risk into the risk analysis process and the formulation of the most appropriate risk management strategies. Therefore, a risk communication strategy should be developed early in the risk analysis

process, i.e. prior to commissioning a risk (e.g. Ch 7 in FSANZ, 2013). To assist risk managers in communicating food safety risk information more effectively, FAO has developed a handbook on the subject (FAO/WHO, 2016).

Communication of relevant scientific information to risk managers by risk assessors can be challenging, especially when there is uncertainty about risk-affecting factors and the ultimate risk to consumers. For this reason, the interaction between risk assessors and risk managers should be ongoing throughout the process. Risk assessors and risk managers should discuss and agree on which stakeholders are consulted throughout the process. While risk managers of the competent authority have the ultimate responsibility for risk management, the risk perception of stakeholders, including industry and consumers, as well as their willingness to operationalise risk management options must be understood. In presenting the results of a risk assessment, the following points should be taken into consideration:

- Results should be presented in a transparent, objective manner. They should be in a form that enables people with little mathematical or statistical background to understand the essential aspects of the risk characterization. For example, a 'technical document' with all modelling details could be paired with a less technical 'interpretive summary'. Additionally, the use of illustrations, graphs and tables for presentation of quantitative information from the model will be more informative than giving just parameter estimates or other statistics as numerical risk outputs.
- Numerical estimates should be supported, and communicated, by qualitative information about the nature of the risk and about the weight of evidence that defines and supports it.
- All assumptions, and their consequences for the risk estimates, sources of variation and uncertainty should be fully presented and acknowledged.
- All the information and data used in the MRA should be explicitly described in the report.
- To ensure transparency, all sources of information or data should be given and cited appropriately and unambiguously in the report and detailed in the references list. A copy of any ephemeral information (e.g. from a Web site) should be saved and filed for reference.
- Any identified needs for additional data should be clearly communicated.

3. Food Microbiological Risk Assessment (MRA)

3.1 Properties and principles of best-practice risk assessments

Codex Guidelines CAC/GL-30 (CAC, 1999) for microbiological risk assessment contain a list of general principles of microbiological risk assessment, including that:

- Risk assessment be objective and soundly based on the best available science and presented in a transparent manner;
- Constraints that affect the risk assessment, such as cost, resources or time, be identified and their possible consequences described;
- Microbiological risk assessment should clearly state the purpose, including the form of risk estimate that will be the output;
- The dynamics of microbiological growth, survival, and death in foods and the complexity of the interaction (including sequelae) between human and agent following consumption (as well as the potential for further spread) be specifically considered;
- Data should be such that uncertainty in the risk estimate can be determined;
- Data and data collection systems should, as far as possible, be of sufficient quality and precision that uncertainty in the risk estimate is minimized;
- The risk estimate should include a description of the uncertainty and where that uncertainty arose; and
- MRA should be conducted according to a structured approach that includes Hazard Identification, Hazard Characterization, Exposure Assessment and Risk Characterization.

The scope of the exposure assessment in terms of content and timeframe should be appropriate to meet its objectives and fulfil the needs of the risk managers. As such, before embarking on a risk assessment, the purpose and scope should be clearly identified and articulated by those who commission it.

Risk assessments should be initiated in response to well-defined risk management questions; where possible these questions should target the evaluation of the specific risk management options under consideration. Discussions with risk managers are needed to define what information is required to support the decisions they have to make and the type of work that needs to be undertaken to provide it. Depending on the risk question(s), this may include provision of surveillance data, or epidemiological data, through to a qualitative risk assessment or a quantitative production-to-consumption exposure assessment. Even if a fully quantitative risk assessment is thought to be necessary, it may be useful to commence with a qualitative approach to better define the nature of the work, the feasibility and the time needed to meet the risk manager's requirements. This again highlights the likely iterative nature of risk assessments.

The risk assessment for microbiological hazards should provide risk managers with a 'best estimate' that is as free of bias as is possible, along with discussion or analysis of the uncertainties and variability in the estimate. Bias describes forms of error that lead to consistent over- or underestimation of the true risk. The basis of the 'best estimate', whether the average risk (mean), or the most likely risk (mode), or some other metric, should be clearly communicated, including a description of why that metric is the best measure of risk. If bias (e.g. the decision to use a worst-case estimate) cannot be eliminated, that bias and the reasons for it should be clearly stated.

Risk assessments should represent the 'real world' situation as closely as possible and reflect the full range of possible outcomes (i.e. probabilities and levels of exposure and consequent risk, e.g. through a distribution of risk per serving), unless risk managers express the need for information on

a particular subset of outcomes, such as 'most likely' or 'worst-case' scenarios. It should be noted, however, that deliberately conservative estimates can reduce the usefulness of the estimate for cost-benefit and cost-effectiveness studies and decrease the ability to describe the uncertainty of the risk estimates. They may be useful in certain situations, however, e.g. to better understand the impact of risk mitigations (see also Section).

Specification of uncertainty and variability are critical in terms of correctly understanding and appropriately using the estimate of risk. It is important to identify variability and uncertainty to the greatest extent possible, discuss their implications for the risk estimate(s) and to provide a description of uncertainty and variability as part of the final risk estimate. Uncertainty and variability are discussed in more detail in Chapter 14.

Independence and functional separation of the risk assessment from the risk management process are highly desirable. Nevertheless, interaction between managers and assessors is also essential to ensure that the risk assessment provides the best possible support for the decision(s) that the risk managers have to make, and to ensure that risk managers understand the principles and assumptions underlying the specific risk assessment.

The need for transparency of the risk assessment requires full documentation of the process. This includes transparency in the process, including calls for data and information, scientific peer review and public review, etc. The report should include an explanation of data used, a description of the models used to assess risk, and explanations of any assumptions made, including the effect of those assumptions on the outcome of the risk assessment.

3.2 Purpose and scope of MRA

Risk assessment is commonly undertaken to help risk managers understand which, if any, intervention strategies can best serve the needs of food safety, or if current risk management actions are adequate.

Before beginning a risk assessment, the purpose and scope should be clearly defined, either explicitly or implicitly through the risk management questions. This may involve a discussion between all relevant parties, including the risk managers, risk assessment team, risk communication specialist, and, when appropriate, relevant stakeholders and interested parties. Definition of the purpose and scope usually specifically identifies the population that should be protected (e.g. general population, young children, pregnant women, immunologically compromised), the stages of the food supply chain that are to be included, as well as the metrics of risks best suited for decision-making. The scope may need to be revised during the preparation of the risk assessment if it becomes evident that the original scope cannot be achieved; any change in scope should be discussed and agreed with the risk manager.

If the risk assessment aims to find the best option to reduce a risk, then a statement of purpose should be prepared to identify all potential risk management options to be considered. The questions and the statement of purpose will, to a great extent, guide the choice of the approach to be taken to characterize the risk. Clearly, this should be done prior to commencing the risk assessment so that the relevant data are gathered, synthesized and analysed in a way that most effectively informs the risk manager. However, if the purpose of the risk assessment is not clear initially, inappropriate data and information may be collected and analysed in ways that, while providing insight into some aspects of the risk, do not provide clear answers to inform the risk manager appropriately.

Risk managers initially define the intended use of a risk assessment in their *Preliminary risk management activities* (CAC, 2007). They may need to interact with risk assessors in an iterative fashion, to refine the specific questions to be answered, the scope, focus or outputs of the risk assessment, possibly throughout the conduct of the risk assessment. Risk managers are expected to ask risk assessors to answer a specific questions about potential risk management options, which when answered, provide the managers with the information and analysis they need to support their food safety decisions (FAO, 2017).

One of the more important preliminary risk management activities is the elaboration of a risk profile (CAC, 2008). A risk profile comprises a systematic collection of the information needed to make a risk management decision and whether a full risk assessment is needed, as outlined by the Codex Guidelines CAC/GL-63 (CAC, 2008). Typically, the risk profile would be a short document, although sometimes it is expanded to a preliminary risk assessment, e.g. the approach used in New Zealand (e.g. Lake and Cressey, 2013) and in the Netherlands' CARMA Project (Bogaardt *et al.*, 2004). This may help to determine the structure of the risk assessment, to fine-tune risk management questions, and assess the feasibility of a more comprehensive risk assessment. While the elaboration of a risk profile is the responsibility of the risk manager it may, in reality, be commissioned out to other parties, including risk assessors.

The purpose and scope of risk assessment can vary depending on the risk managers' questions. The following sections contain a discussion of three possible approaches to 'risk assessment'. No 'correct' approach can be recommended or specified: the choice of approach depends on the risk assessment question, the data and resources available, etc. The three approaches, considered as examples, are:

- Estimating a baseline risk
- Comparing risk intervention strategies
- Research-related study or model

3.2.1 *Estimating 'baseline risk'*

A common and practical starting point for a risk assessment is to estimate the existing level of risk, often termed the 'baseline risk', i.e. the level of food safety risk posed without any changes to the current system. This risk estimate is most frequently used as the baseline against which intervention strategies can be evaluated, if desired (Figure 3). Using the current risk level as a baseline has several advantages, among them being that it is the easiest to estimate the effect of changes by estimating the magnitude of the risk after the changed conditions relative to the existing level of risk. This approach implicitly accepts the starting point of any risk management actions as being changes to the current system. For some purposes, a baseline other than the existing level of risk might be used as a point of comparison. For example, the baseline risk could be set as that which would exist under some preferred (e.g. least costly) risk management approach, and the risk under alternative approaches compared with that.

Estimating a baseline risk may not be for the immediate purpose of managing the risk so much as to measure or bound the severity of a food safety problem and hence decide whether the risk merits further management. Whilst in theory it may not be necessary to determine a baseline risk to evaluate intervention strategies, it is nonetheless almost always carried out in practice. Baseline risk does not always need a fully detailed farm-to-fork risk assessment and could instead rely mostly on epidemiological data and knowledge of underreporting rates (see also Section 3.2.2).

3.2.2 *Comparing risk management strategies*

Ideally, agencies with responsibility for safety of foods would consider all possible risk management interventions along the food chain without regard to who has the authority to enact them. This objective has led to the creation of integrated food safety authorities in many nations and regions. For example, Berends *et al.* (1998) considered the likely effects on exposure (i.e. *Salmonella* contamination of pork retail cuts) under different intervention strategies, covering various steps in the farm-to-retail continuum.

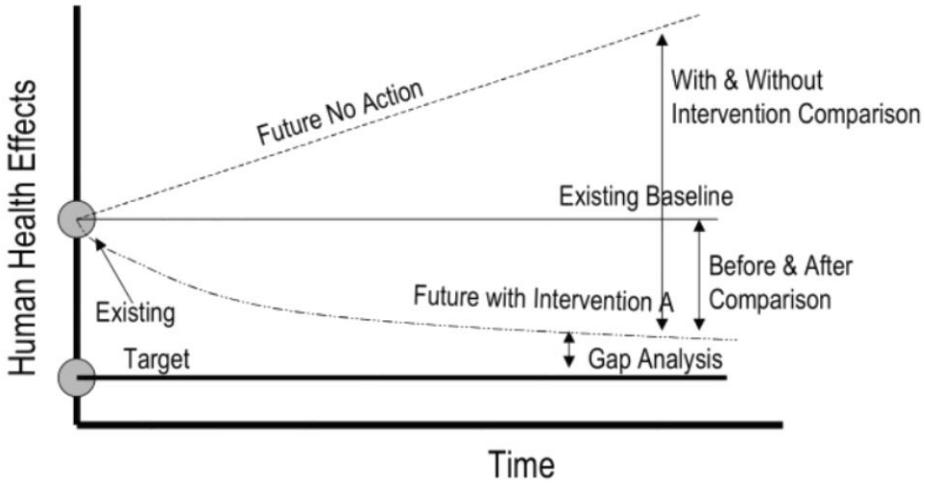
A farm-to-table model may be most appropriate for this purpose. In practice, however, the scope of the assessment may be limited to those sections of the food chain within the risk manager's area of authority, but a more comprehensive risk assessment might identify relationships outside that area of authority that would motivate the risk manager to seek the authorisation required to intervene effectively or to request others with authority to take appropriate actions. For some risk questions, analysis of epidemiological data or a model of part of the food chain may be adequate. As discussed elsewhere, some risk assessments may be undertaken to ascertain whether existing food safety regulations and existing intervention strategies are adequate, or most appropriate, and if they require review.

Evaluations of putative risk management actions are often based on comparisons of a baseline risk estimate with a forecast risk that could result from pursuing various alternative strategies (FAO/WHO, 2009b; USFDA, 2005) as shown in Figure 3, sometimes called 'what-if' scenarios. One includes a future with no new intervention (the future status quo), the other a future with a new intervention. Initially, a baseline model (i.e. the 'without intervention' scenario) is constructed and run to give a baseline estimate of risk. Then the model or selected model parameters are changed to determine the probable effect of the putative intervention(s).

The differences between the two risk estimates offer indications of the public health benefits of the proposed intervention(s) and, if possible, could also indicate the costs required to attain them. Combinations of interventions can be investigated in a similar fashion, to determine their joint effect, in an effort to find the optimal strategy. However, risk managers should also consider sub-optimal strategies in the broader context, i.e. taking into account the multi-dimensional nature of risk management (FAO, 2017). In some cases, it is possible to estimate the change in risk without producing an estimate of the baseline risk, but caution must be used in these cases. For example, a risk assessment might determine that it is technically feasible to reduce a particular risk one-hundred-fold, but if this risk was negligible at the start, then reducing it one-hundred-fold may not be a worthwhile course of action.

There are many ways to approach an evaluation of risk management options, including gap analysis, before and after comparison, and with and without comparison (as illustrated in this example). The risk estimates, special studies, economic and environmental analyses, opinion surveys, analysis of the legal implications of proposed actions, and the like will vary from case to case. Not all of these elements are within the domain of risk assessment, but a few generic steps in the process can be identified. These include:

- Describe the existing baseline risk condition, i.e. the current state of the risk, given the intervention strategies already in place.
- Describe the most likely future condition in the absence of a change in risk management intervention, i.e. the 'without' condition. Every option is evaluated against this same 'without' condition, labelled 'Future No Action' below. This future may exhibit an increasing, decreasing, flat or mixed trend.
- Describe the most likely future condition anticipated with a specific risk-management intervention in place, i.e. the 'with' condition. Each intervention has its own unique 'with' condition: in the example below, it is labelled 'Future With Intervention A'.
- Compare 'with' and 'without' conditions for each intervention option.
- Characterize the effects of this comparison: not all effects are equal in size, some are desirable, others are not.



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678 *Figure 3: 'With' and 'without' intervention scenarios and changes in risk over time*
679 *(FAO/WHO, 2009a, Box 2.2).*

680 ### 3.2.3 *Research-related study or model*

681 Research findings are needed to do good risk assessment. There are a number of large
682 microbiological risk assessment models in existence that have been initiated as academic exercises
683 (Guo *et al.*, 2015; Pang *et al.*, 2017; Van Abel *et al.*, 2017). These models have helped advance the
684 field of microbiological risk assessment by allowing us to see what techniques are necessary,
685 developing new techniques, and stimulating research that can now be seen to have value within a
686 risk assessment context. In some situations, those models have subsequently been used by risk
687 managers to assist in risk management decisions. Such models have also made apparent the changes
688 in collection and reporting methods for microbiological, epidemiological, production, dietary and
689 other data that would make the data more useful for risk assessment.

690 Risk assessment is also a very useful aid in identifying where gaps in knowledge exist and thus where
691 additional information is needed. A risk assessment may be undertaken specifically or incidentally to
692 identify research needs, to establish research priorities, and to help design commissioned studies.
693 Experience with microbiological risk assessments has proven these assessments to be valuable in
694 aiding the understanding of complex systems. The very process of systematically investigating a food

chain has contributed to the ability to both appreciate and understand the complexity of the systems that make up the food chain.

3.3 The role of best- and worst-case scenarios

It may be useful to evaluate the best- or worst-case scenarios to get a sense of 'how good could it be' or 'how bad could it be' as a filtering technique or as part of a risk profile. The worst-case scenario can be used to filter out whether a risk or an exposure pathway is worth worrying about. No further analysis is necessary if the most pessimistic estimate shows the risk level to be below some threshold of interest (e.g. a negligible-risk level or an acceptable level of risk as defined by a competent authority).

Conversely, a best-case scenario can be used as a preliminary filter of possible risk management options. The risk manager can discount any options for which the most optimistic estimate of the benefits the options could offer does not justify the cost of that option.

Best- and worst-case scenarios operate like extreme 'what-if' scenarios. Where there is considerable but quantified uncertainty about a model parameter, a value is used that gives the required extreme. This will usually be an extreme value from the uncertainty distribution of the parameter, e.g. its 1st or 99th percentile. Where there is uncertainty about exposure pathways and risk attribution, the extreme risk estimate is achieved by picking the most pessimistic (or optimistic) pathway: for example, 'imagine that all *Salmonella* came from chicken'.

Potential problems with worst-case analyses include focusing the analysis on the consequences of the worst case, without the context of the probability of that worst-case scenario occurring, and the difficulty in specifying the conditions that might lead to the worst (or best) case: absolute extremes may be limited only by our imaginations no matter how unlikely. Conversely, when parameter values or exposure pathways are known with considerable certainty, they should be used to avoid exaggerating the extreme scenario beyond what is likely. The concept of *compounding* or *compounded conservatism* is well known in chemical risk assessment. While a detailed explanation of the concept is beyond the scope of this document, the interested reader is directed towards scientific literature (Bogen, 1994; Burmaster and Harris, 1993; Cullen, 1994), including Cassin *et al.* (1996) who specifically discuss the dangers of compounding conservatism in quantitative microbial risk assessment.

3.4 Assessing the results of a risk assessment

When undertaking a risk assessment, the risk assessor needs to consider two basic probability concepts that can affect the outcome. The first is the apparently random nature of the world; the second is the level of uncertainty about how the real world is operating. Together, they limit the ability to predict the future and the consequences of decisions made that may affect the future. Inevitably, a risk assessment will not have included all possible information about a risk issue because of limited data access (for example, time constraints for the collection of data, or unwillingness of data owners to share information) or because the data simply do not exist. Complying with all the requirements of transparency, of describing model and parameter uncertainties, and all the explicit and implicit assumptions, does not necessarily communicate to risk managers the degree of confidence that the risk assessor has in the results of the risk assessment or limitations in its application. Thus, risk assessors must clearly explain the level of reliability, or confidence, they attach to the risk assessment results. The reliability of the results depends on the extent of variability and uncertainty in the model outcomes.

All assumptions should be acknowledged and made explicit in a manner that is meaningful to the risk manager. In particular, it should be explained what the assumption is, why the assumption was made and why it is appropriate, and what the expected effect is if the assumption doesn't hold.

The process of microbiological food safety risk assessment is most affected by uncertainty: uncertainty about what is really happening in the exposure pathways resulting in human illness; uncertainty about processes that lead from ingestion through to infection and illness and that dictate the severity of the illness in different people; and uncertainty about the values of the parameters that would describe those pathways and processes. In general, risk assessments should be as simple as possible whilst meeting the risk manager's needs. The MRA should strive to balance greater detail and complexity (e.g. through addressing more questions or alternative scenarios) against having to include more assumptions that this would entail, because more assumptions increase the uncertainty and decrease the reliability of the conclusions. A draft risk assessment, in which the data gaps and assumptions are clearly identified, may elicit new information, if distributed widely to important stakeholders.

Sometimes what is known at a particular time is insufficient for a risk manager to be comfortable in selecting a risk management option. If the risk manager's criteria for making a particular decision (i.e. the 'decision rule') are well defined, a risk assessment carried out based on current knowledge can often provide guidance as to what, and how much, information would make a decision clearer. Another benefit of the risk assessment methodology is that it provides a basis for rational discussion and evaluation of data and potential solutions to a problem. Thus, it acts to create consensus among stakeholders around risk management strategies or helps to identify where additional data are required.

The purpose of a risk assessment is to help the risk manager make a more informed choice and to make the rationale behind that choice clear to all stakeholders. Thus, in some situations, a very quick and simple risk assessment may be sufficient for a risk manager's needs. For example, imagine the risk manager is considering some change that has no cost associated with it, and a crude analysis demonstrates that the risk under consideration would be 10-90% less likely to occur following implementation of the change, with no secondary risks. For the risk manager, this may be sufficient information to authorize making the change, despite the high level of uncertainty and despite not having determined what the base risk was in the first place. Of course, most risk issues are far more complicated, and require balancing the benefits (usually human health effect avoided) and costs (usually the commitment of available resources to carry out the change, as well as human health effects from any secondary risks) of different intervention strategies. Thus, depending on the specific question posed, an exposure estimate may be enough to allow comparison between different interventions to be made, allowing the risk manager to make an informed decision.

In the process of performing a risk assessment one usually learns which gaps in knowledge are more, and which are less, critical and some of those uncertainties are readily quantified with statistical techniques where data are available, which gives the risk manager the most objective description of uncertainty. If, however, a risk assessment assumes a particular set of pathways and causal relationships that are incorrect, then the assessment will be flawed. This is clearly different from variability and uncertainty (Chapter 14) and should be avoided as much as possible.

3.5 Choosing the type of risk assessment to perform

Risk assessments methods span a continuum from qualitative through semi-quantitative to fully quantitative. These approaches may vary in their key attributes, for example: quality of risk inference, timeliness, complexity, assessor training requirements, and data requirements (note that

a scientifically sound risk assessment requires collection of suitable information/data/assumptions which are documented and fully referenced and synthesized in a logical and transparent manner, regardless of where on the methodology continuum the approach sits). All are valid approaches to food safety risk assessment, but the appropriateness of a particular method ultimately depends on the ability of the risk assessment to address the specific risk question and that it is "fit-for-purpose" to support the risk management decision. A benefit of risk assessment as a whole is that solutions to minimize risk often present themselves out of the formal process of modelling risk, whether the risk assessment that has been conducted is qualitative, semiquantitative, quantitative, or a combination with elements spanning the continuum.

- **Qualitative Risk Assessment:** Qualitative risk assessments are descriptive or categorical treatments of information. A qualitative assessment may be undertaken as part of a first evaluation of a food safety issue, to determine if the risk is significant enough to warrant a more detailed analysis; this again highlights that risk assessments tend to be, and frequently are, iterative. Nevertheless, a qualitative exposure assessment alone may, in some circumstances, provide all the decision support needed by the risk manager. If a more detailed analysis is warranted, then a fully quantitative assessment is usually the preferred approach if data, time and resources are available to support it.
- **Semi-Quantitative risk assessment:** Semi-quantitative risk assessment provides an intermediary level between the textual evaluation of risk that characterises qualitative risk assessment and the numerical evaluation of quantitative risk assessment, by evaluating risks with a score. It offers a more consistent and rigorous approach to assessing and comparing risks and risk management strategies than qualitative risk assessment and avoids some of the ambiguities that a qualitative risk assessment may produce. It does not require the same mathematical skills of quantitative risk assessment, nor does it require the same amount of data, which means it can be applied to risks and strategies where precise data are missing.
- **Quantitative risk assessment:** Quantitative risk assessments provide numerical estimates of risk, although most models use combinations of mathematics and logic statements. Quantitative risk assessments require the development of mathematical models in which all relationships between factors affecting exposure can be quantified or explained using logical tests and conditional statements. An exposure estimate may be combined with a mathematical function that quantifies the dose-response relationship to provide an estimate of risk.

It should be noted that there is a gradation of model types from qualitative to fully quantitative and while such classifications may be helpful, they are not strictly defined categories.

The importance of matching the type of risk assessment to its purpose has been emphasized previously. The USA National Advisory Committee on Microbiological Criteria for Foods noted (USNACMCF, 2004):

> *"Risk assessments can be quantitative or qualitative in nature, but should be adequate to facilitate the selection of risk management options. The decision to undertake a quantitative or qualitative risk assessment requires the consideration of multiple factors such as the availability and quality of data, the degree of consensus of scientific opinion and available resources."*

The Australian National Health and Medical Research Council (NHMRC, 2018, p38) cautions that:

"Realistic expectations for hazard identification and risk assessment are important. Rarely will enough knowledge be available to complete a detailed quantitative risk assessment. ... Staff should have a realistic understanding of the limitations of these predictions, and this should also be conveyed to the public."

The decision on the appropriate balance of the continuum of methods from qualitative to quantitative will be based on several factors, including those considered below.

3.5.1 *Consistency*

Risk assessments should limit subjectivity as far as possible and aim for consistency. On the one hand, qualitative and semi-quantitative risk assessment can be made simple enough to be applied repeatedly across a range of risk issues, whereas quantitative risk assessment is more driven by the availability of data and may have to employ quite disparate methods to model different risks. Subjectivity can occur across the spectrum. Qualitative risk assessment is more prone to subjective judgements involved in converting data or experience into categories such as 'high', 'intermediate' and 'low' because it may be difficult to unambiguously define these terms, so repeatability of an analysis by others is less certain. On the other hand, quantitative risk assessments may involve subjective choices regarding model form and data analysis, e.g. in approaches to the selection and analysis of data. In all cases the basis of these judgements can, and should, be documented in a way that enables others to understand the reasoning and replicate the results.

3.5.2 *Resources*

Some basic capacities are needed to conduct MRA or its components. Risk assessments conducted at the international level (e.g. JEMRA) can assist countries by providing modules or building blocks that can be adapted or modified to suit other exposure or risk assessments. For example, FAO/WHO's Food Safety Risk Analysis Tools website[3] contains a risk assessment tool for *Cronobacter* spp. in powdered infant formula and a risk management tool for the control of *Campylobacter* and *Salmonella* spp. in chicken meat, and the US FDA's FDA-iRISK® tool[4] allows sharing of risk assessment models/modules. However, it must be remembered that the risk assessment usually requires also some country- or region-specific data.

The basic capacities needed include:

- **Access to expertise**. While the assessment may be carried out by one individual or a small team, access to a range of other expertise, from multiple disciplines, usually is needed. Depending on the task, this is likely to include trained risk assessors, modellers, mathematicians, statisticians, microbiologists, food technologists, animal and plant health specialists, agriculture technologists, human and veterinary epidemiologists, public health specialists, and other experts as needed. Quantitative risk assessments typically require that at least part of the assessment team have rigorous mathematical training. If this resource is in limited supply, then this may make qualitative risk assessment more practical, provided the risk question is amenable to this approach. Note that, though qualitative risk assessments may not be demanding in terms of pure mathematical ability, they place a considerable burden of judgement on the analyst to combine evidence in an appropriate and logical manner, and the technical capability necessary to collate and interpret the current scientific knowledge is almost the same.

[3] www.fstools.org accessed 20 June 2019
[4] irisk.foodrisk.org accessed 20 June 2019

- **Informed risk managers and policymakers** who are aware of the need for, use of and limitations of risk assessment, working in the context of an appropriate risk management framework, whether in government or industry. This framework must facilitate data collection, decision-making and implementation.
- **Financial and human resources** to complete the risk assessment in a timely manner and to an acceptable level that provides useful support for risk management decisions. For very large MRA projects, a dedicated project manager may be desirable.
- **Communication channels**. Good communication is needed between technical experts, risk managers and the risk assessors to facilitate efficient exchange of data and knowledge.
- **Information technology**. Computing facilities, both hardware and software and access to appropriate information networks are needed, to collect, collate and process data, and to provide outputs in a form suitable for communication of results. This should include access to international networks and databases, including access to scientific publications.
- Where data on microbiological hazards are not available, **the capacity to conduct surveillance for microbiological hazards**, including access to microbiologists, epidemiologists, trained field staff and competent laboratories, is needed.

While the above list is an ideal, benefits can also be obtained from conducting more modest risk assessments, but still according to the principles in these Guidelines, even from teams with limited expertise. To assist groups with fewer resources, communication (e.g. including training, mentoring and technology transfer) with more established groups should be actively encouraged.

With respect to scientific publications, access to subscription-based journals has repeatedly been identified as a substantial limitation in many developing countries. It is worthwhile to note that Research4Life (www.research4life.org) provides developing countries with free or low-cost access to academic and professional peer-reviewed content online. To assist the risk assessors with their tasks, a range of software tools have been developed, including those listed by Bassett *et al.* (2012) and those at the QMRA Wiki.[5] These tools are not necessarily specific to food safety risk assessments, although a range of food safety specific models and tools are also identified, covering areas of risk ranking, predictive microbiology, specific risk assessment and sampling tools. The idea and application of predictive microbiology in exposure assessment described in Section 12.2, with examples of the necessary fine detail given in Section 12.2.

3.5.3 *Theory or data limitations*

Quantitative risk assessments tend to be better suited for situations where mathematical models are available to describe phenomena, e.g. Dose-Response models, and where data are available to estimate the model parameters. If either the theory or data are lacking, then a more qualitative risk assessment is appropriate.

3.5.4 *Breadth of application*

When considering risks across a spectrum of hazards and pathways, there may be problems in applying quantitative risk assessment consistently across a diverse base of theory and evidence, such as comparing microbiological and chemical hazards in food. The methodologies and measurement approaches may not yet be able to provide commensurate risk measurements for decision-support where scope is broad.

[5] http://qmrawiki.canr.msu.edu/index.php accessed 18 June 2019

3.5.5 *Speed*

Qualitative and semi-quantitative risk assessments generally require much less time to generate conclusions compared with quantitative risk assessment. This is particularly true when the protocols for qualitative and semi-quantitative risk assessments have been firmly established with clear guidance in the interpretation of evidence. There may be some exceptions where the process of qualitative risk assessment relies on a process of consultation (e.g. when relying heavily on structured expert elicitation) that requires considerable planning, briefing, and scheduling. Quantitative risk assessment may take longer to develop; if it is to be repeated once the model is established, then the speed to generate conclusions is similar to qualitative or semi-quantitative approaches.

3.5.6 *Transparency*

Transparency, in the sense that every piece of evidence and its exact effect on the assessment process is made explicit, is more easily achieved by quantitative risk assessment. However, accessibility, where a large audience of interested parties can understand the assessment process, may be better achieved through qualitative or semi-quantitative risk assessment. Quantitative microbiological risk assessment often involves specialized knowledge and a considerable time investment. As such, the analysis may only be accessible to specialists or those with the time and resources to engage them. Strict transparency is of limited benefit where interested parties are not able, or find it excessively burdensome, to understand, scrutinize and contribute to the analysis and interpretation, and errors in quantitative risk assessments may also be more difficult to find. Qualitative or semi-quantitative approaches may be easier to understand by a larger range of stakeholders, who will then be better able to contribute to the risk analysis process.

3.5.7 *Stage of analysis*

Qualitative and quantitative risk assessment need not be mutually exclusive. Qualitative risk assessment is very useful in an initial phase of risk management to provide timely information regarding the approximate level of risk and to decide on the scope and level of resources to apply to quantitative risk assessment. As an example, qualitative risk assessment may be used to decide which exposure pathways (e.g. air, food, water; or raw versus ready-to-eat foods) will be the subject of a quantitative risk assessment.

Where available, comparing the outputs from both approaches, or from different stages of the analysis, may help the detection of errors that may have been made in either assessment.

3.5.8 *Responsiveness*

A major concern often expressed in regulatory situations is the lack of responsiveness of risk assessment conclusions when faced with new evidence. Consider a situation where a risk assessment has been carried out with older data indicating that the prevalence of a pathogen is 10%. After the risk assessment is published, it is found that the prevalence has been reduced to 1%. In most quantitative risk assessments, there would be a clear effect of the reduced prevalence on the risk characterization. In some qualitative risk assessments, this effect may not be sufficiently clear. Qualitative risk assessments, particularly where the link between evidence and conclusion is ambiguous, may contribute to foster or support this lack of responsiveness. The unresponsiveness can generate mistrust and concern for the integrity of the risk assessment process.

4. Hazard Identification

Hazard identification (HI) is conventionally the first step in risk assessment. For the purposes of the Codex guideline , hazard identification related to food safety is defined as "the identification of biological, chemical and physical agents capable of causing adverse health effects and which may be present in a particular food or group of foods" (CAC, 1999). In particular, for microbiological agents "the purpose of hazard identification is to identify the microorganisms or the microbial toxins of concern with food" (CAC, 1999). In general, hazard identification is largely a qualitative examination of the foodborne hazard and associated potential adverse health outcomes due to specific foodborne exposure, which is supported by a critical review of knowledge about the hazards and/or food in question. In the context of MRA, the term *hazard* encompasses any microbiological agent able to cause harm, including bacteria, viruses, parasites, fungi, algae, including their toxins and metabolites, as well as prions.

4.1 Objectives of hazard identification

The main purpose of hazard identification is to identify the microbiological hazard(s) found in food that is/are the cause of specific adverse health outcomes. Since a wide range of microbiological hazards can cause food-borne illness, hazard identification should identify whether a potential hazard is realistic for the food product of interest. In some situations, i.e. depending on the risk managers' questions, the hazard characterization may include a list of hazards and therefore, the final product of the hazard identification procedure is a practical list of microbiological hazards related to the specific food product (e.g. FAO/WHO, 2006a, 2007).

4.2 The process of hazard identification

Essentially, the hazard identification serves to establish the hazard as likely or real in the food product and to document the important information known about the relationships and interactions between the hazard, the food (including intrinsic characteristics, environmental factors and production conditions) and host, as well as their relationship to human illness (Figure 4). There is some overlap between the information collated as part of the hazard identification step and the exposure assessment and hazard characterization steps – the hazard identification may provide only a general overview, while the latter steps document the detailed information, e.g. extent of exposure to the hazard and dose-response relationship. The information is documented to address general questions as part of microbiological hazard identification, including:

- What is/are the hazard(s) of concern associated with specific food in question?
- Is the hazard of concern to public health and what is the likelihood of the hazard causing an adverse health effect?
- What is the population at risk?
- What is the epidemiological evidence, including outbreaks and sporadic illness, that this hazard poses a potential risk in the food product of concern?
- What adverse health effects could be associated with the exposure to the hazard and through what mechanisms?
- What host factors and life stages could potentially influence the sensitivity and the type and severity of adverse health outcomes among population at risk?
- How do common exposure pathways link the adverse health effects with the hazard?
- How often does the hazard occur in the food product of interest?
- How do environmental conditions affect the hazard's transfer and fate along the exposure pathway?

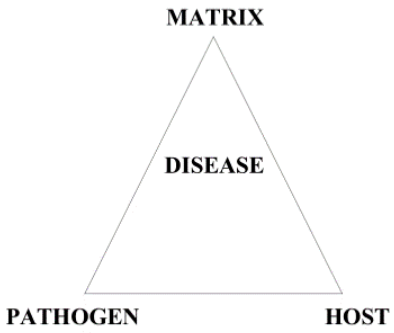


Figure 4: The epidemiology triangle (modified from Coleman and Marks, 1998).

A wide range of microbiological hazards are associated with food-borne illness. To identify the most significant hazards in the food of concern, characteristics of a range of hazards can be collectively evaluated, including inherent properties of hazards such as invasiveness, virulence, pathogenicity, natural reservoir, transmissibility and resistance to environment factors and interventions as part of the food supply chain.

In addition, hazard identification highlights issues such as sensitive populations, acute versus chronic disease and other complications such as long-term sequelae for later detailed consideration in the hazard characterization (Chapter 6). Sensitivity to infection depends on the integrity of the hosts' immune system, the virulence/potency of the hazard and exposure levels of the hazard. The integrity of hosts' immune system can be influenced by life stage and health conditions. For example, young children and the elderly may be more sensitive to microbiological infection compared to young healthy adults due to their immature or compromised immune systems, leading to more serious and longer-lasting health outcomes. The exposure level of and ability of a hazard to elicit an adverse health effect at the time of consumption can be cumulatively affected by a series of environmental conditions throughout the food chain. The physical and chemical property of the food matrix may influence the hazards' survival and persistence and these, together with growth, inactivation and survival characteristics of the hazard can be elaborated in the exposure assessment (Chapter 5). For example, the presence of fat component of chocolate protects *Salmonella* against thermal inactivation. The transmission and fate of a hazard may be influenced by the complex interaction between the hazard and various intermediate vectors. For example, bacterial pathogens from food-producing animals may reach the human population directly through the consumption of contaminated animal foods or indirectly through the consumption of crop products contaminated due to the land application of animal wastes.

Sometimes evidence clearly identifies the significance of foodborne transmission for specific microbiological hazards and which foods are implicated before a microbiological risk assessment is conducted. In this situation, less effort can be expected in the investigation of the causal relationship between the occurrence of adverse health outcomes and the exposure to the foodborne hazard. Conversely, emerging hazards are continually being identified through the mechanism of acquiring new traits. Through vertical or horizontal transfer of genetic traits among microorganisms, newer pathogenic or opportunistic strains can be consistently produced, which could result in new microbiological hazards with higher virulence and/or persistence to various environmental conditions. In this situation, when a particular food is suspected, more thorough investigation is needed to indicate whether the hazard is likely associated with the food product of interest.

4.3 Data sources for hazard identification

A large amount of relevant evidence-based information needs to be collected, appraised and interpreted in hazard identification. The main types of data sources providing useful information to the hazard identification process are as discussed in Chapter 10.

Epidemiologic data from disease monitoring programs, or investigations of foodborne outbreaks are often the first well documented indication of a food safety problem with adverse effects associated with a pathogen. Food contamination surveillance data, together with product/process evaluations can aid the identification of hazard-food combinations. Evidence from these sources is usually quantitative (i.e. includes information about the concentration or number of units of the hazard in the food), which may also provide information, particularly feeding into other steps of microbiological risk assessment such as exposure assessment and/or the establishment of dose-response relationship. Whole genome sequencing (WGS) is being used increasingly for foodborne pathogen surveillance, outbreak investigation and contamination source tracking throughout food supply chains (Rantsiou *et al.*, 2018, WHO, 2018). Clinical research usually provides qualitative data, highlighting the mode of action with which the hazard affects the host, such as through the action of toxins, either in the food or, alternatively, through infectious mechanisms. Inferences from microbiological and clinical studies can be used to support the epidemiological and observational evidence. More details regarding the strength and limitation of different data sources can be found in Chapter 10.

5. Exposure Assessment

5.1 The Process of Exposure Assessment

Codex defines exposure assessment as "the qualitative and/or quantitative evaluation of the likely intake of biological, chemical, and physical agents via food as well as exposures from other sources if relevant." (CAC, 1999). Consequently, exposure assessments are often specific to the production, processing and consumption patterns within a country or region.

Exposure assessment may be undertaken as part of a risk assessment, or it can be a stand-alone process, such as when there are not enough data or information available to undertake a dose-response assessment (i.e. a Hazard Characterization) or when the risk management question only involves quantifying or seeking ways to minimize exposure. The process of exposure assessment can be, and usually is, iterative. Discussions between risk managers and risk assessors may lead to a refinement of the initial question or problem statement to be addressed in the risk assessment, or consultation with other parties may result in the availability of new information, that can in turn lead to revision of assumptions or to further analysis. Also, non-governmental bodies such as food industry may use exposure assessment as a stand-alone process or as part of an MRA approach to assess the safety of their food products, specifically as part of food innovation research and before putting products on market (van Gerwen and Gorris, 2004; Membré and Boué, 2018; Pujol *et al.*, 2013).

The goal of an exposure assessment may be to provide an estimate of the level of exposure to a hazard in a given population but may also be limited to evaluation of one or a few processing steps. The risk manager may also wish to limit the scope to specific regions, or populations, or periods of time. This again reinforces the need for the risk managers to clearly articulate their needs to the assessors, including the level of detail required in the exposure assessment, and any constraints that would limit the range of management options. For example, when a comparison of potential mitigations is requested, the managers should provide an indication of the measures they would consider or have available for the reduction of exposure from a particular source, as well as any other sources, that would not be acceptable under any circumstances.

Once there is a clear understanding of the requirements of the exposure assessment in relation to risk management, the next step is to consider the factors that have a direct effect on consumer exposure to the hazard. These including frequency of consumption of the product or commodity; pathway and frequency and levels of contamination with the hazard; the range of doses; and factors that affect it (potential for microbial growth, inactivation during cooking (or other processes), meal size, seasonal and regional influences, etc.).

In addition, the exposure assessment should describe the relevant pathways of exposure. Scenarios can be constructed to predict the range of possible exposures. For example, if the purpose of the risk assessment is to identify and compare different mitigation strategies to be used from production to consumption, then the entire production-to-consumption pathway has to be addressed (Figure 5). In other cases, only the pathways from retail to consumers may be relevant, thus if the purpose of the exposure assessment were to reach a decision on the maximum tolerable level of a pathogen in a ready-to-eat product at the point of sale, the exposure assessment would be used to determine the potential for further increase or decrease in exposure due to normal consumer handling, such as time and temperature of storage, effect of cooking or other food preparation steps, potential for cross-contamination in the home, etc.

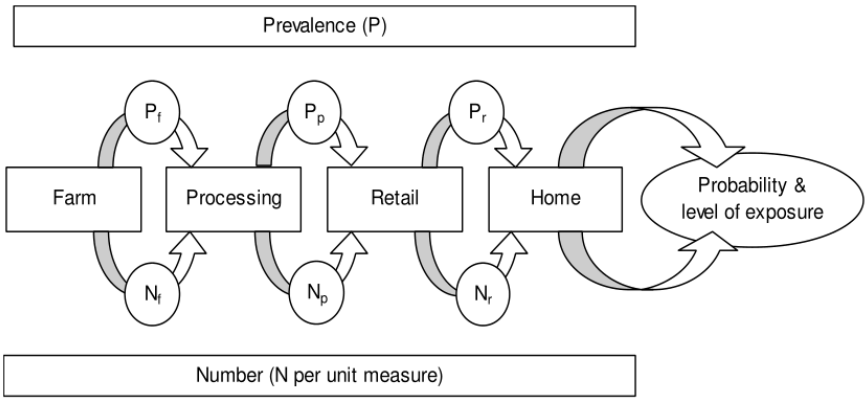


Figure 5: An example of an overview of the conceptual model to describe the exposure pathway for a production-to-consumption exposure assessment. To assess exposure, it is necessary to consider both the probability that a unit of food is contaminated with the hazard (denoted P, for 'prevalence'), and the level, or number, of that hazard in the food (denoted N) at the time of consumption. For microbial hazards, in particular, both prevalence and number can change as the commodity is further processed, and as time elapses before the product is finally consumed.

The level of detail required in the different pathways reflects the question asked and the information needed by the risk managers and may be modified based on the information available. If it has been shown, for instance, that the prevalence and/or numbers of a specific pathogen differs within a specific commodity according to the type of abattoir, type of processing, type of storage at retail, etc., such information might influence the level of detail required and the selection of pathways in the exposure assessment. Food supply pathways can be multiple and complex, for example, 'ready-to-eat' meals are a synthesis of food components (e.g. meat, vegetable and dressing) that arise from different pathways.

Risk managers may have specific questions concerning specific processes, such as organic farming, logistic slaughtering, i.e. order in which animals are slaughtered (e.g. Nauta *et al.*, 2009), or imported foods (e.g. Skjerve, 1999) that they want to be addressed. Accordingly, these specific interests would need to be taken into account in selecting the pathways to be considered or modelled and the types of data to be included.

5.2 Modelling Approaches

5.2.1 *Introduction*

The goal of exposure assessment is to deduce, from the available information, the probability and magnitude of exposure to the hazard. Detailed exposure data, characterizing the extent of microbiological hazards present in foods at the time of consumption, are usually not available. Thus, exposure assessment will often rely on a model, encompassing knowledge of the factors and their interactions that affect the number and distribution of the hazard in foods, to estimate exposure at consumption. This chapter is primarily concerned with development and application of models used as part of the exposure assessment. General data needs and sources are considered in greater detail in Chapter 10.

A model can be defined as 'the description of a system, theory, or phenomenon that accounts for its known or inferred properties and may be used for further study of its characteristics' (McMeekin *et al.*, 2008). Often the model is a simplified description of some more complex system or phenomenon. Models are also used to communicate an understanding, or hypothesis, concerning some aspect of reality that may or may not be able to be directly observed. Thus, another description is that a model is 'a hypothesis or system of beliefs about how a system works or

responds to changes in its inputs' (Cullen and Frey, 1999). That hypothesis or description can be expressed in words or 'as a system of postulates, data, and inferences presented as a mathematical description of that entity or state of affairs'.[6] When developing a model – whether it is a full risk assessment or any part thereof – it is important to ensure that the model is fit-for-purpose. As a result, a model should be as simple as possible, but as complex as necessary.[7]

Among the benefits of a model is that it can be used to predict the outcome of events that have not occurred, or have not been observed, e.g. the probability of infection from low doses. However, a fundamental rule of modelling is that no possibility should be modelled that could not actually occur (Vose, 2008). In the context of exposure assessment, the models synthesize data and knowledge from other observations about the pathways of exposure, the behaviour of microbial hazards in foods, patterns of consumption, and so on, to infer what would, or could, happen in other circumstances of interest. Models can be used to interpolate among discrete values of observed data and, in some circumstances, to extrapolate beyond the range of observations. In either case, the validity of the interpolation or extrapolation depends on validation of the model (see Sections 16.2).

There is a spectrum of approaches available for exposure assessment, ranging from qualitative to fully quantitative in nature. Quantitative exposure assessments may, in turn, be deterministic or stochastic, with the later encompassing and representing variability and uncertainty in the data and knowledge as fully as possible (see Chapter 14).

Although qualitative exposure assessments lack numerical precision, they are still valuable and may, in some circumstances, provide all the decision support needed by the risk manager. Also, as an example, a qualitative assessment may be undertaken as part of a Risk Profile, to determine if the risk is significant enough to warrant a more detailed analysis. This again highlights that risk assessments tend to be, and frequently are, iterative. If a more detailed analysis is needed to answer the risk question and to provide the needed decision support for the risk manager, then a fully quantitative assessment is usually the preferred approach if data, time and resources are available to support it.

5.2.2 *Qualitative and semi-quantitative exposure assessment*

A qualitative assessment may be developed by assigning descriptive ratings of probability and severity such as 'negligible', 'low', 'medium' or 'high' to the exposure factors (ACMSF, 2012; Fazil, 2005).

As noted in Section 3.5, semi-quantitative exposure assessment provides an intermediary level between qualitative and quantitative exposure assessment. It does not require the same mathematical rigor as quantitative exposure assessment, nor does it require the same amount of data, which means it can be applied to exposure and exposure minimisation strategies where precise data are missing. See also Sections 9.1 and 9.2 for more detailed discussion of these qualitative and semi-quantitative risk assessment approaches. Examples of semi-quantitative risk assessment approaches, including for exposure assessment, being used to make risk management decisions (Cardoen *et al.*, 2009; Hald *et al.*, 2006; Omurtag *et al.*, 2013; Sumner and Ross, 2002).

[6] https://www.merriam-webster.com/dictionary/model accessed 26 Nov 2018

[7] A rephrasing of Einstein's principle "A scientific theory should be as simple as possible, but no simpler."

5.2.3 *Quantitative exposure assessment*

As noted above, quantitative exposure assessments provide numerical estimates of exposure. They require models to be developed, in which all relationships between factors affecting exposure are described mathematically.

As well as mechanistic or empirical, quantitative models can be divided into two categories (Bassett *et al.*, 2012):

1. *Deterministic*, sometimes also referred to as 'fixed-value' or 'point-estimate' and which in some situations can be solved analytically, and
2. *Stochastic*, sometimes also referred to as 'probabilistic'. In some limited circumstance, these models may be able to be evaluated analytically, though most are more likely to need to be evaluated using 'Monte Carlo simulation', requiring computers and software.

In a mathematical model, 'input' variables are those that determine the type and magnitude of the response, or 'output', variables. The output variables in exposure assessment are the frequency and magnitude of exposure of consumers to the microbiological hazard in the food of interest. Depending on how much of the food supply chain is included in the exposure assessment, input variables could include factors such as time, temperature, production volume and dilution during processing (see data sources in Chapter 10). If a modular process framework is utilised for the exposure assessment (e.g. Figure 5), then outputs from one module are the inputs for the next module. 'Parameters' quantify the input variables and can be fixed values or distributions. For example, while bacterial growth may be proportional to temperature, a mathematical model is needed to relate growth rate and temperature (see Chapter 11). The parameters of that model could be fixed for a specific strain of a hazard but will differ between species and perhaps even for different strains of the same species. In the latter situation the between-strain variability in growth rates, as a function of temperature, could be described by a distribution.

Stepwise approach to quantitative risk assessment

As described above, exposure assessments often involve description of very complex systems, where each variable may not contribute equally to exposure and where not all the desired data may be available. In the context of MRA, van Gerwen *et al.* (2000) suggested that, under such conditions, it could be beneficial to conduct an exposure assessment in a series of stages of increasing complexity/sophistication. Similar approaches have been suggested by the US EPA (2006) and Cullen and Frey (1999) and may be particularly useful when there is an urgent need for an estimate of exposure or risk. A rough estimate is first made of the order of magnitude that individual factors or parameters may contribute to exposure or consequent risk. This could be considered as part of a risk profile. For those factors that contribute most significantly, a more detailed assessment is performed, or more data are gathered and combined in, for instance, a deterministic approach. Where relevant, an even higher level of detail can be achieved using a stochastic approach. Van Gerwen *et al.* (2000) propose that, when using a stepwise approach, both efforts and resources are focused where they add most to reducing uncertainty in the exposure estimate.

5.2.4 *Modelling the production-to-consumption pathway*

Introduction

As noted above, the methods by which exposure is estimated depends on the combination of risk management questions being addressed and the amount of data and other resources available, such as expertise and time. An exposure assessment that considers the events from agricultural

production through to consumption will demand the most time and resources. Such an exhaustive approach may be appropriate if:

- the risk management questions require consideration of all stages, e.g. the effectiveness or feasibility of mitigation at the farm, estimates of exposure in final product as consumed, and
- there are sufficient data, knowledge, time and expertise to enable consideration of each stage.

A generic full production-to-consumption pathway is outlined in Figure 5. Various approaches for modelling of this pathway are outlined below. It is important to emphasise that the final approach utilized depends on the risk management questions being addressed and is therefore assessment-specific, thus the following should be viewed as guidelines, or examples, rather than as being prescriptive.

Model development

'Conceptual model' is a term used to describe the understanding of the routes by which the population of interest is exposed to the hazard of concern, including all the factors and their interactions that affect the probability and level of exposure. The conceptual model may be expressed in text, diagrams, as a mathematical model or a combination of these. There is no preferred method to develop and describe the conceptual model. Rather, whatever form the conceptual model takes, it should adhere to the principles and guidelines for the conduct of microbiological risk assessment (CAC, 1999). For the purposes of communication of the conceptual model to non-mathematicians, a diagrammatic representation may be useful and more readily understood than a text-only description, or the mathematical model alone.

Different approaches can be used to develop the conceptual model. The *Event Tree* approach describes a scenario from a contamination event to a defined end-point of the assessment (Roberts, Ahl and McDowell, 1995), e.g. consumption. This approach serves to describe or identify the most likely pathways that lead to contamination and subsequent disease and may identify variables in need of further data or modelling. Conversely, the *Fault Tree* approach begins with the occurrence of a hazard and from there describes the events that must have occurred for the hazard to be present (Roberts, Ahl and McDowell, 1995). This approach can provide a framework to analyse the likelihood of an event by determining the complete set of underlying conditions or events that would allow the given event to occur (Jaykus, 1996).

Additional approaches to modelling used in assessments of microbial food hazards include the *Dynamic Flow Tree* model (Marks *et al.*, 1998) and the *Process Risk Model* (PRM) (Cassin, Paoli and Lammerding, 1998). The former emphasizes the dynamic nature of bacterial growth and incorporates predictive microbiology using statistical analysis of data, whereas the latter focuses on the integration of predictive microbiology and scenario analysis to provide an assessment of the hygienic characteristics of a manufacturing process.

A general framework is the *Modular Process Risk Model* (MPRM) (Nauta, 2001, 2008; Nauta *et al.*, 2001), which can be thought of as an extension of the PRM approach (Cassin, Paoli and Lammerding, 1998). The fundamental assumption of the MPRM approach is that at each of the steps or key activities in the various intermediary stages from production to consumption, at least one of several processes can be assigned. These processes can be divided into microbial and product handling processes. The microbial processes include growth and inactivation, and the food and product handling processes include mixing of units, partitioning of units, removal of parts of units and cross-contamination of organisms among units. The transmission of infection among live animals during

primary production could be viewed as an additional biological process, which provides the starting estimates of prevalence in a full production-to-consumption model.

When developing mathematical models, the model structure can facilitate or hinder probabilistic (stochastic) analysis and sensitivity analysis. It is recommended that the models should be formulated such that independent variables affecting exposure are clearly specified and in such a way that paired data for each iteration of the model can be stored for all inputs and outputs for which sensitivity analysis is required. Depending on the modelling approach selected, a one-to-one relationship may not be possible when partitioning or combining of units is included (e.g. Kiermeier, Jenson and Sumner, 2014).

The definition of 'unit' is crucial when modelling the processes from production to consumption. A unit is defined as a physically separated quantity of product in the process, for example an animal, a (part of a) carcass, or a package of ground beef, a milk tank or a bottle of milk. It may be that one unit from primary production is also the consumer package (e.g. an egg or whole chicken), but most examples are more complex, e.g. beef carcass transformed to ground beef burger. In this case, units have to be redefined at each partitioning or mixing stage. Both the number of organisms (N) and the prevalence (P) (see Figure 5) should be treated as uncertain and variable throughout the model. This makes it possible to assess the uncertainty and variability in the final exposure, and thus the uncertainty in the final risk estimate.

It should also be noted that prevalence and concentration are related. If the (mean) concentration of the pathogen in a batch of food were low (e.g. 1 cell per 5 kg) the prevalence of contamination will depend on the size of the unit of food. If the unit size were 100 g, then it would be expected that one in 50 units would contain a pathogen, i.e. the prevalence would be 2%. But if the unit size were 500 g, then it would be expected that one unit in 10, on average, would contain a pathogen, i.e. the prevalence would be 10%. If the unit size were 5 kg, then it would be expected that the prevalence would be 100%. However, in practice, because the cells would not be expected to be perfectly evenly distributed, the prevalence would be less than 100%, because some units would contain more than one cell and, consequently, some others would contain none. It is possible to estimate the concentration in a batch from the prevalence and size of positive samples, provided that not all samples of that size are 'positive', and this approach based on the same statistical principles as the 'most probable number' technique used in microbiology (Cochran, 1950). For a good exploration of the distribution of microbes in food (Bassett *et al.*, 2010).

Approaches to mathematical modelling of microbial growth and inactivation and their application are outlined in Sections 12.1 and 12.2. It is difficult to suggest a general model framework for cross-contamination but useful discussion of this topic can be found in Schaffner (2003, 2004).

As noted above, different modelling approaches have been proposed and used. The approach used therefore depends on the perspective of the assessor and on the problem being modelled, as indicated by the risk question. Discussion of modelling strategies for the stages from production to consumption is presented below; which stages to include will depend on the scope and purpose of the risk assessment.

Primary production (farm)

The main focus of the primary production or "farm" stage of the exposure assessment is to estimate the prevalence and concentration of the microbiological hazard in the population or crop or product of interest; the same approach applies for wild capture or harvest situations. For example, this might be prevalence and contamination levels per live cow, per bird, per homestead, per kg of lettuce

leaves, per apple or per vat of raw milk. Within the model for animal products, it is important to differentiate infection and colonization from contamination of skin surfaces. These may of course be dependent on each other, such as where excretion by infected or colonized animals may result in contamination of that animal as well as any other animals in the group.

Recognizing and incorporating dependencies between variables in a risk assessment model is an important aspect of constructing robust and logical models. This is particularly important when constructing stochastic models in which the variables in the model are described as a distributions of possible values, because the values are selected randomly from each variable's distribution. Thus, it is can occur that impossible outcomes can be modelled if a value is selected from one distribution that could never occur with a value selected for another variable. Such model iterations can greatly distort the results of stochastic models, unless the dependencies between variables are explicitly recognised and included in the modelling. These issues are further exemplified in Section 12.2.

The level of detail required in the farm model depends on the risk questions being addressed and specifically if on-farm control is of relevance or possible. This detail will relate to whether or not transmission of infection or contamination is included. The model of Hartnett *et al.* (2001), for example, considers transmission on farm while the models of Cassin *et al.* (1998) and USDA/FSIS (2001) do not. Similarly, FAO/WHO (2009c, 2009d) concerning the risk to human health from *Campylobacter* in broiler chickens included on-farm modelling of infection and transmission from fomites, contaminated water, other birds, etc. Conversely, FAO/WHO (2002a) were unable to usefully model pathways of transmission of *Salmonella* on farms.

It must be remembered that animals or plants harvested for food may become contaminated/ infected from many sources including irrigation/drinking water, contaminated feed, vermin and feral animals, bird faeces, etc. or from the water itself in the case of fish and especially shellfish.

Transport to processing plants

Transport from primary production to processing can also be included in the exposure assessment, because cross-contamination of primary production units can occur, or infection can spread between units in close proximity, and can cause an increase in overall microbial load. Stress during transport of animals can lead to increased faecal shedding and dissemination of pathogens to uninfected animals. Microbial loads on produce can also increase due to microbial growth during transport (Arthur *et al.*, 2007; FSIS, 2001).

Processing

The stages in processing need to be defined before a model can be constructed to describe the changes in prevalence (see also comments above about the interplay between prevalence, sample size and contamination level) and in the numbers of organism. There can be many stages in food processing though not all will necessarily have a strong influence on the ultimate risk to human health. Cassin *et al.* (1998), for example, identified 36 distinct processing operations during the slaughter of beef cattle. It is unlikely that all these stages will be followed by all processors, and an added difficulty is elaborating processing scenarios that are both representative of the majority of processors, yet take into account differences between processors. Flow diagrams developed for HACCP systems can be a useful source of information on process steps and conditions.

Modelling of processing involves:

- Considering the way in which the unit size changes from stage to stage and how this affects prevalence and concentration of organisms;

- Considering changes as a result of cross-contamination, without unit size changing; and
- Considering changes due to microbial growth or inactivation.

Much effort is expended during food processing operations to minimize microbial growth and/or to maximize microbial inactivation (e.g. using heat), or to prevent cross-contamination from other material or the processing environment through cleaning and sanitation. Important factors controlling the extent of growth and inactivation are the duration of conditions and severity of treatment (particularly temperature) prevailing during the process. The MPRM methodologies for mixing, partitioning and removal can be used to model the effects of changes to unit size (Bassett *et al.*, 2010; Nauta, 2008).

Studies of the effects of some processing steps on the levels of microbiological hazards often report on the result of analysis of 'before and after' samples, such as the number of organisms contaminating a broiler carcass before and after a stage, e.g. defeathering. Dogan *et al*. (2019) evaluated the effectiveness of intervention strategies in processing plants to protect the safety of chicken consumers, through the development of quantitative exposure assessment models. The same approach was applied by Smith *et al*. (2013) to evaluate the relative effects of pre-harvest and processing interventions on public health risk for the consumption of ground beef and beef cuts contaminated with *Escherichia coli* O157:H7 in Canada. When the process is not relevant to the decision, then detailed modelling is not needed or desired. The reduction (or increase) in numbers is, thus, sometimes modelled using a 'black box' approach whereby the changes are modelled, without attempting to describe any of the underlying microbial processes. Alternatively, mechanisms of recontamination of products in factory environments are discussed in den Aantrekker *et al.* (2003). Similarly, where changes are due to growth or inactivation, the effects of process duration and conditions on microbial numbers can be estimated using well-established predictive models (Tenenhaus-Aziza and Ellouze, 2015; e.g. Zwietering and Hasting, 1997a, 1997b).

Normally, results from 'before' and 'after' samples are reported in terms of $\log_{10}$ populations. Caution is needed, however, when modelling cross-contamination when the initial contamination levels are reported as $\log_{10}$ populations. For example, if a cross-contamination event adds 1,000 organisms per unit (i.e. 3 $\log_{10}$) to a unit containing 100 organisms (i.e. 2 $\log_{10}$) it is incorrect to conclude 2 $\log_{10}$ + 3 $\log_{10}$ = 5 $\log_{10}$ (or 100,000 organisms per unit). The correct calculation involves converting the log counts to their arithmetic value and then adding the total numbers, i.e. 100 + 1,000 = 1,100, which means the final contamination is 3.04 $\log_{10}$ organisms per unit, from the original 2 $\log_{10}$. This is because contamination is an additive process. In contrast, microbial growth is a multiplicative process because growth is exponential, *i.e.* where the increase is based on the initial number of organisms in the product and numbers change exponentially over time (such as microbial growth or inactivation). In those cases, the log values can be added, e.g. 2 $\log_{10}$ initial plus 3 $\log_{10}$ growth = 5 $\log_{10}$ at the end of growth, because *every* cell initially present increased in number by 1000-fold. These are examples where errors would result in causal relationships that are incorrect and thus resulting in a flawed assessment; such errors should clearly be avoided.

The variation and uncertainty associated with modelling the change in numbers should also be given careful consideration. When choosing the approach, careful thought should be given to what the data represent (variation, uncertainty or both) and how representative they are. For example, a problem with modelling the results of carcass samples is ensuring that the sampled portion is representative of the entire carcass. An example of a remedy to this challenge is to estimate the magnitude of the bias in a separate study and include this in the model. A practical corollary of this is that if contamination on the carcases is unevenly distributed, then when the carcase is broken down

into smaller pieces, not all will carry the same level of contamination. This is a good example of the consequence of partitioning and where contamination on each smaller unit may differ. Consequently, the prevalence and distribution of contamination levels on sub-units would need to be described.

During processing, formulation of products can be altered. Such alterations may change the potential for microbial growth, e.g. adding growth inhibiting compounds (e.g. salt or organic acids) to processed food, drying/water removal leading to reduction of water activity, acidification during fermentation, addition of water, etc. Similarly, packaging can influence the potential for microbial growth, or inactivation, or cross-contamination. Thus, changes in the condition of the product over time have to be modelled as part of exposure assessment.

Processing often involves steps designed to reduce or eliminate microbial loads so that not only the expected magnitude of the reductions due to these steps, but also their uncertainty/variability, will need to be modelled Also, if the initial contamination levels are low, and a typical unit size is small, then not all units will contain the hazard so that increased risk (in the absence of cross-contamination) can only come from growth in the units that *do* contain a viable infectious unit.

Post-Processing

The post-processing environment includes storage and transport/distribution, retail display and handling, food service operations and home kitchens. These steps can allow microbial growth, cross-contamination, but also hazard reduction through cooking, physical removal of contamination, etc. Table 1 lists some of the factors of the post-food-processing environment that could influence hazard frequency and level of exposure.

While some of these environments may differ in some respects, there are often important similarities and some data collected in one environment may be suitable surrogates for assessing changes in exposure in other environments (e.g. cross-contamination from cutting boards).

Table 1: Examples of factors of importance when determining the impact of the post-processing environment on the level of exposure.

Factor	Example
Temperature	
Static (though variable)	Refrigerated storage temperature
Dynamic	Cooling times and temperatures for cooked food
Product formulation	pH and water activity of the food, preservative compounds (sorbate, lactate, nitrite, nisin, etc.)
Biotic factors in food (inter-species competition)	Relative level of spoilage or other microorganisms on the product compared to pathogens, e.g. fermented food, lactic acid bacteria in vacuum-packed foods.
Time	Time on a salad bar, time between cleaning the blade of a processed meat slicer
Cross-contamination	
Foods	*Salmonella* transfer from chicken
Surfaces	
Food contact surface	*Campylobacter* transfer to cutting board
Hand contact surface	*Listeria* transfer to refrigerator door
Cleaning (sponge, cloth)	*E. coli* survival on sponge

Factor	Example
Hands	*Staphylococcus* transfer from hands
Bodily orifices	Hepatitis A virus from diarrhoea via hands, fomites
Survival on surfaces	*Shigella* survival on stainless steel
Cleaning	
Washing	Effect of washing, soap and water for 20 seconds
Sanitizing	Effect of 200 ppm chlorine
Discards	Decision to use lunch meat beyond its use-by date

Transport and storage post-processing can include:

- Transport from the processor to a food service establishment or retail outlet, possibly via a distribution centre, and subsequent storage
- Warehousing
- Retail storage and retail display
- Storage and handing in food service
- Transport from retail to the home by the consumer and subsequent home storage; this type of transport and storage is likely to be less well controlled: most consumers do not have refrigerated vehicle and frequent access to domestic upright domestic refrigerators means frequent loss of temperature control

Transport and storage conditions may also be less-well controlled in different regions, e.g. in countries where street food vending is common, street vendors often lack the facilities for proper temperature control, or insect or vermin control. In addition, farmers markets may pose additional challenges in terms of temperature control during transport, storage and retail (Young *et al.*, 2017b).

In general, relatively little information is available in the published literature on transport temperature and durations. With respect to transport between processor and retailers (or further processing), information on durations is likely known by the processors, indicating the need for good risk communication and involvement of stakeholders early in the risk assessment process. However, less is known about the temperature profile during transport, although the increasing availability of relatively cheap data loggers, possibly GPS enabled, are helping to remedy this situation (e.g. Sumner, 2016). Similarly, not many published research articles exist about retail or food service storage. An example of temperature data collection is provided by Ecosure (2008), who collected data on cold temperature storage of products in various areas of retail stores (which is available in raw spreadsheet format).

Less is known about the treatment of food during transport to the home, likely related to the logistical difficulties of obtaining such data. Ecosure (2008), however, also collected data from consumer volunteers on transport to the home. The volunteers also reported how product was transported, the temperature in the part of the vehicle where product was located as well as the outside temperature, and time between purchase and placing each product into the refrigerator/freezer at home. Similarly, Kim *et al.* (2013) reported on temperature profiles of various food products during transport to the home.

Using information about duration and temperature at each stage during post processing, predictive microbiology models may be used to predict the growth and inactivation of the hazard. Depending on the hazard and the durations involved, care may be needed to include the effects of shelf life

(limit on total duration between production and consumption) and competing and spoilage bacteria, where possible (Section 12.2).

Cross-contamination

Post-processing environments can be much more complex than processing environments because of the variety of foods involved (restaurant menus, for example, may have dozens of items, and a cafeteria may have hundreds); the complexity of food preparation operations (highly non-linear when compared with food processing operations); differences in preparation setting (home *vs* food service); differences between operations in terms of physical layout (one kitchen *vs* another); and level of training (new worker *vs* highly experienced). The need to evaluate how microorganisms are transmitted along the food chain has motivated the study of other phenomena besides growth and death. Cross-contamination has been recognized as an important factor directly related to outbreaks of food-borne diseases and food spoilage and therefore may need to be included in the exposure assessments (Possas *et al.*, 2017).

The potential complexity involved in modelling cross-contamination during food preparation is shown in Figure 6 for the act of preparing a cooked chicken product and a lettuce salad.

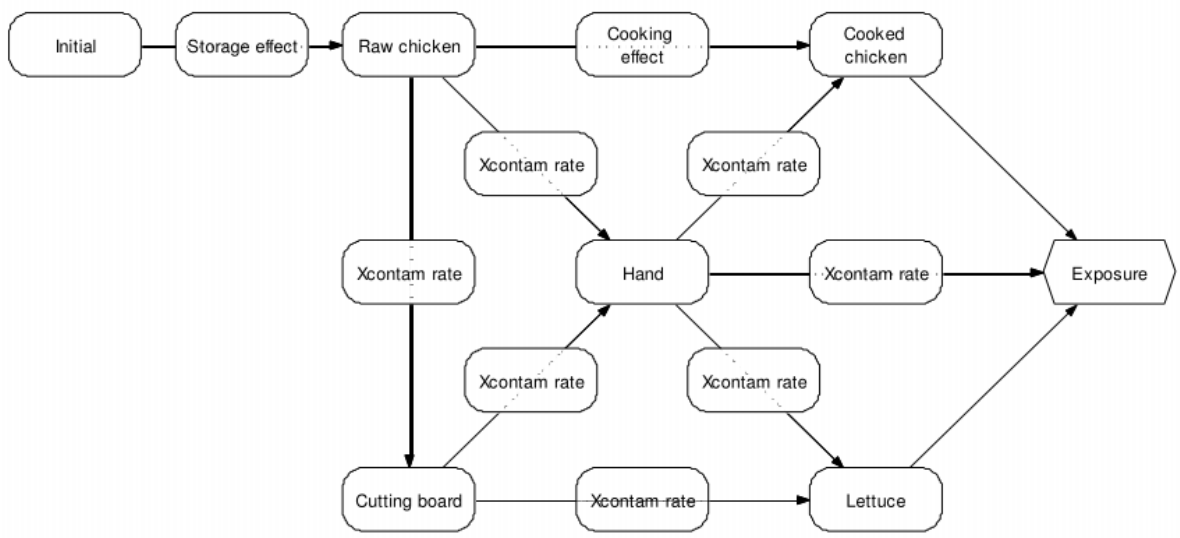


Figure 6: An example 'influence diagram' of a model of a cross-contamination pathway for the preparation of cooked chicken and lettuce salad. (Xcontam = cross-contamination).

Despite its complexity, a number of simplifying assumptions are made in Figure 6:

- The lettuce and the individual preparing the food do not contribute any microbiological hazard to the exposure except for cross-contamination originally arising from the chicken;
- Hands and cutting board are the only cross-contamination vehicles, and other kitchen surfaces (knives, plates, sponges, towels, aprons, counter-tops, etc.) do not contribute to exposure;
- No changes in microbial numbers occur during any step except storage and cooking (e.g. bacterial populations on cutting board do not change); and
- The frequency at which each event occurs is not specified, and in fact multiple contamination events may occur in any food preparation procedure.

Some of the simplifying assumptions listed above can be shown to be false in many situations. One simplifying assumption is that no changes in microbial numbers occur during any step except storage

and cooking, but growth on contact surfaces does occur and may be important. The rate of potential growth on contact surfaces can be used to dictate the minimum time interval between successive cleanings of equipment in contact with raw product. Surfaces that become contaminated with films of nutrient-rich liquids from raw product may contain bacterial pathogens which could grow in the film. This surface is then replenished with new material from each subsequent unit and can promote cross-contamination to other units. Consider that a work-shift may be 4 to 8 hours in duration and that the working environment is maintained at 10-15°C (such temperatures are maintained in some food processing operations because at lower temperatures workers became less dextrous and are more likely to have accidents and injuries). Based on estimates from published predictive models, pathogens could increase by 10- to 1000-fold in some products, e.g. *Vibrio parahaemolyticus* on fish and shellfish (100- to 1000-fold), *Listeria monocytogenes* on smoked fish (10-fold) and *E. coli* on raw meat (10-fold). Predicted increases may be quite different under processing settings where food products are moved on and off the preparation surface throughout the shift, each potentially depositing and/or removing some of the contamination.

Another difficulty in populating the diagram in Figure 6 with real numbers and mathematical relationships is a lack of published data on many consumer storage practices and on cross-contamination rates. The large uncertainty and variability associated with preparation and cooking practices has been recognized in national and international reports of exposure assessments. The FAO/WHO exposure assessment models for *Salmonella* spp. and *Campylobacter* spp. in broilers suggest that cross-contamination during preparation and cooking can affect exposure (FAO, 2001; FAO/WHO, 2002a; WHO, 2001).

Despite the large number of studies reviewed by Pérez-Rodríguez *et al.* (2008) the authors concluded that: "The main objective and challenge when modelling bacterial transfer is to develop reliable mathematical models … However, with today's knowledge, such models are a Utopia, since information is imprecise and scarce, and data show major experimental errors." Possas *et al.* (2017) have updated the available cross-contamination modelling approaches in foods as well as the available evaluation methods for model robustness.

Given the limited amount of reliable data available for quantifying the effects of cross-contamination, most exposure assessments have considered this event in a simplistic manner, for example, by including a limited number of pathways, and by estimating both the probability of transfer and the numbers of organisms transferred (e.g. Hartnett, 2002). Other approaches have also been adopted including the Health Canada *Campylobacter* risk assessment, where the transfer of organisms in the drip fluid was also considered (Fazil *et al.*, 1999). Schaffner (2004) modelled the cross-contamination of *Listeria* species using a quantitative mathematical model using Monte Carlo simulation techniques. Chen *et al.* (2001) quantified the probability of bacterial transfer associated with various steps in the food preparation process and provided a scientific basis to include cross-contamination in the exposure assessment with the aim to support risk management strategies to reduce or prevent the cross-contamination in the kitchen. Zilelidou *et al.* (2015) evaluated the cross-contamination phenomena that might take place between cutting equipment and leafy vegetables in common households or in food preparation environments and provided quantitative data regarding the transfer rate of *E. coli* O157:H7 and *L. monocytogenes* from contaminated lettuce to kitchen knives and subsequent transmission to fresh lettuce. Other studies have evaluated the cross-contamination rates of *L. monocytogenes* (Gallagher *et al.*, 2016), *Salmonella* (Smid *et al.*, 2013), *Campylobacter* (Hayama *et al.*, 2011; Moore, Sheldon and Jaykus, 2003; Mylius, Nauta and Havelaar, 2007), and *E. coli* O157:H7 (Jensen *et al.*, 2015; Pérez-Rodríguez *et al.*, 2011).

In summary, post-process food preparation is a highly complex, and poorly characterized, part of the production-to-consumption food chain. Limited data are available, and numerous data gaps have been identified. Given the complexity of this part of the food chain, research to better understand and describe these processes is ongoing. Publication of the results of that research will contribute to improved exposure assessment where cross-contamination may be an important route of exposure. However, cross-contamination is initially a *redistribution* process and, unless that redistribution alters the fate of the hazard, that is, either due to growth or reduction the benefits of cross-contamination modelling, prediction the risk to consumers, or elucidating practical risk management options, should be carefully considered.

5.2.5 *Consumption*

To characterize the risk from exposure to microbiological hazards in food, it is necessary to know the amount of food consumed and how often it is consumed and by whom, and the form in which it is consumed (raw or cooked) because susceptibility is variable and some groups (e.g. very old, very young) are more likely to develop illness from food-borne hazards.

The specific characterization of food consumption patterns used in the MRA depends on the question to be answered by the assessment, as well as the food consumption data that are available to the risk assessor (Chapter 10). The data collated and published by WHO through the GEMS cluster diets[8] may be useful when no other data are available. However, care needs to be taken, as for any consumption data, to ensure correct interpretation (see below).

Modelling the amount of food consumed

When modelling food consumption, it is important for risk assessors to understand the specifics of how the food consumption data were collected and analysed, and to clearly describe how these data were used in the model, including any assumptions used in arriving at the estimates.

The important aspects of calculating the amount of food consumed, particularly when using results from food consumption surveys, include:

- the population divisor, *i.e.* whether the total consumption amount is divided by the total population (amount per capita) or only those who consumed the food (amount per consumer);
- the frequency of consumption (per day/week/month/year); and
- the amount consumed per consumption event.

These are discussed below.

Amount per capita vs per consumer

The per capita amount is calculated by dividing the total amount of a food by the total number of people in the population. The per consumer amount is calculated by dividing the total amount of food only by the number of people who actually consumed the food.

For foods that are consumed regularly by the majority of the population (e.g. bread), the per capita and per-consumer amounts will be nearly equal. For foods that are consumed by fewer individuals (e.g. raw oysters), the per capita and per-consumer amounts will be quite different.

[8] http://www.who.int/nutrition/landscape_analysis/nlis_gem_food/en/ accessed 29 Nov 2018

For example, consider that 10 million kg of a food are consumed by 10% of the population, which consists of 10 million people. The average consumption per capita equals 1 kg, while the average consumption per consumer equals 10 kg.

Amount per year, per day or per eating occasion

Consumption may be calculated as the amount per time-period (e.g. year, month, week or day) or per eating occasion. Definition of the consumption period is particularly important in MRAs because acute, rather than chronic, exposure is of concern. In contrast, chronic exposure may be relevant for some microbial toxins that are released into foods before consumption, e.g. mycotoxins, and in such situations chemical risk assessment approaches are appropriate ((e.g. see FAO/WHO, 2009e)). Often, the dose of microbial toxins is stoichiometrically related to the level of contamination of the food by the toxigenic organism.

National food production statistics (e.g. FAOSTAT[9]) generally report an amount of food produced per year. Care needs to be taken to fully understand the values. For example, if the amount of fish caught is reported, does the amount relate to whole fish landed, or does it relate to the amount after gilling and gutting? Clearly, amounts ultimately consumed need to be adjusted to remove inedible parts of the food and any losses incurred during processes. Similarly, food wastage in the supply chain due to spoilage or other reasons needs to be accounted for if possible. For highly perishable products (meat, fish, fruits, salad vegetables, etc.), this may be as high as 20 to 25% of production (Gustavsson, Cederberg and Sonesson, 2011).

A consumption amount may be estimated by dividing the total annual amount (per capita or per consumer) by the average number of eating occasions. Returning to the example above, if the food product is thought to be consumed daily then the average amount would equal 10kg divided by 365 days, or about 27.4g per day. This amount may be too small to be realistic and hence the data and assumptions for the calculations need be re-assessed and adjusted, if necessary. For example, it may be that a typical amount consumed in a meal is closer to 100g and hence this would imply that the food is consumed about 100 times per year, or approximately once every 3-4 days, or that not all members of the population eat that food. Meal size and consumption data may be available from surveys for some countries.

Food consumption surveys of individuals allow much more flexibility in estimating the consumption amount. Survey results are frequently summarized and reported on the basis of daily consumption. If the raw data from the survey are available, then it may also be possible to calculate the amount of food consumed per eating occasion (depends on coding system and questions in the questionnaire) and the frequency of consumption. The basis for consumption is particularly important when considering foods that may be consumed more than once in a single day. For example, if a person drinks a 250-ml glass of milk at each of three meals, the amount per meal would be 250 ml, whereas the amount per day would be 750 ml.

When calculating daily food consumption from food consumption survey data, it is important to note whether the amount was calculated as an average over all days of the survey or for only the days on which a food was consumed. As an example, in one study, five days of dietary records were collected for individuals participating in the survey. From those data, consumption could be calculated as consumption on the days the food was actually consumed or as the average, or total, over five days for which each person participated in the survey. Of course, different people will consumer different amounts per meal, e.g. young children or the elderly might have smaller portion

[9] http://www.fao.org/faostat/ accessed 29 November 2018

sizes than young adults. In this case, serving size can be modelled as a distribution, if the data are available. In general, all other things being equal, larger serving sizes would be correlated with slightly higher risk of illness. If there is a correlation between serving size and particular consumer characteristics, these correlations can also be modelled to reflect the differential risk to different consumers.

Importance of characterizing the distribution of contamination

The importance of modelling the distribution of the number of organisms in a food will depend on the dose-response relationship for that organism. If a high level of growth occurs in a single unit of food prior to consumption, only one person is likely to be affected because that single unit of food will be consumed by one person. Assuming that there are more than enough cells of the hazard present to cause infection in most individuals, if that same dose were spread equally over 100 servings, then the same dose might be enough to infect many of the 100 consumers (assuming a pathogen with a high probability of infection per infectious particle, e.g. norovirus). Conversely, for a pathogen with a very low probability of infection per cell (e.g. *Listeria monocytogenes*), the predicted risk to the entire population from the exposure is largely independent of the distribution of doses among units of food and is effectively estimated from the average dose. This is because there is, effectively, a direct proportionality between the dose and probability of infection for all realistic doses (see Chapter 6) and for those realistic doses the probability of infection is much less than one. In this situation, there is less need to characterize the distribution of the pathogen among different servings. Nauta (2000) provides advice on modelling distribution among individual servings. However, the risk to an individual is dependent on the dose ingested which, in turn, is dependent on the serving size.

Consumption frequency

The frequency of consumption refers to how often an individual consumes a food in a specific period. In MRAs (e.g. FAO/WHO, 2002a; USDA-FSIS, 2001; USFDA/FSIS, 2003; USFDA, 2005), frequency of consumption has been expressed in a variety of ways:

- Number of days per year on which the food is consumed.
- Number of eating occasions over a year:
    - annual number of meals,
    - number of times the food is consumed per year, or
    - number of 100-g portions consumed in a year.

The number of days of consumption during the consumption survey period can be determined directly from the survey results; from that, an annual number of days of consumption may be extrapolated.

The number of meals, eating occasions or individual food items may be calculated directly from the survey results, if the survey covers more than one day per individual. Alternatively, data from single 24-hour recall surveys can be combined with information from food frequency surveys on the proportion of the population who 'usually' consume a food in a given period to estimate the annual number of consumption days.

It may be possible to refine or verify the estimated frequency of consumption by combining food consumption data with other industry information, such as annual sales volume or market share information (Chapter 10). For example, if the food consumption data report the frequency of consumption of a broad category such as cheese, market share data may be used to predict the frequency of consuming a particular type of cheese (e.g. Camembert). Note that it might be

reasonable to assume that the amount of cheese consumed is similar across types of cheese although the frequency differs by cheese type. As noted above, consideration should be given to the proportion of production that is never consumed due to spoilage, not sold by specified 'use-by' or 'best-before' date, or due to other forms of 'wastage'.

A useful 'reality check' is to combine food consumption amounts with frequency of consumption, and number of consumers to calculate approximate production volumes, taking into account wastage, imports and exports, etc. These estimates should be comparable to actual production volumes and big discrepancies may indicate that some of the estimates or assumptions are not valid.

Considerations and challenges in modelling food consumption

There are a number of aspects of food consumption data that should be considered when developing the food consumption model.

Extrapolating data from results of food consumption surveys

Food consumption surveys generally collect information from a subset of the population (e.g. van Rossum *et al.*, 2011). If the sample is representative of the total population and statistical weights developed for the survey are used in the data analyses, survey results may be used to predict food consumption patterns for the population as a whole.

For MRAs, it may be important to estimate the consumption by sensitive population groups, such as the elderly or the immunocompromised. In the absence of specific data for these groups, it is usually assumed that their consumption patterns are the same as the normal, healthy population of the same age and gender.

Infrequently consumed foods

Estimates of consumption based on a small number of observations (i.e. small number of food consumption records) will be less reliable than estimates based on larger samples. For this reason, care should be taken when interpreting and extrapolating survey results for infrequently consumed foods, even if the overall survey size was large and survey weights are used in the data analysis.

If the survey data are used to model consumption for an infrequently consumed food, it is important that the consumption amount be calculated from the day or eating occasion on which the food was consumed, rather than as the average over all survey days.

Food consumed as discrete items vs components of mixed dishes

Some foods may be consumed both as discrete items and as components of combination foods or food mixtures. For example, milk may be consumed as a beverage, but also as an ingredient (often in small amounts) in many food items. The normal usage of those foods can also affect hazard levels, e.g. milk consumed in meals may be heated which could reduce pathogen numbers compared to milk consumed as part of a cold milk drink. When modelling food consumption, it is important to know whether the consumption estimate includes all sources of the food or only the amount of food consumed as a discrete item. If the consumption estimate includes consumption of the food from all sources, it may be necessary to consider the 'recipes' for foods containing that ingredient. This will not only allow estimation of the total consumption from all sources, but also the form in which the food is eaten, including the effects (if any) of food preparation steps for combination foods that might affect the risk. Similarly, it may be necessary to estimate from the total consumption only that proportion consumed in a form in which the hazard could be present, such as unpasteurized juice or milk, or hot dogs eaten without reheating. As another example of the effect of mixing and partitioning, while consumption data for shell eggs may indicate that a person eats 60 g of shell egg per day, in some situations the serving may have been made from many eggs combined, such as

scrambled eggs in an institutional setting. In such a case, many consumers might be exposed to a single contaminated egg compared to another situation where a single consumer eats the entire contaminated egg.

Aggregation or grouping of foods

If the risk assessment is focused on food groups rather than individual foods, consideration should be given to the way in which foods are aggregated for estimating consumption. The average consumption amount for a food category is affected by the number of foods it represents and how similar the foods are in terms of the usual amount and frequency of consumption. If the foods are too dissimilar, the average amount and frequency of consumption may be misrepresented. For example, if fluid milk and cheese are grouped together as 'dairy products', the consumption amounts may be quite different, and the average consumption will likely underestimate consumption of milk and overestimate consumption of cheese. Again, if a food category includes seasonal items as well as foods that are available year-round, the frequency of consumption may be under- or over-estimated for the seasonal foods. Some consumption surveys do, however, identify seasonal effects, e.g. by sampling individuals at many times throughout the year.

6. Hazard Characterization

6.1 The Process of Hazard Characterization

Codex defines hazard characterization as "the qualitative and/or quantitative evaluation of the nature of the adverse health effects associated with biological, chemical and physical agents, which may be present in food" (CAC, 1999). Hence, the hazard characterization provides a description of the adverse effects that may result from ingestion of a hazard, whether that is a microorganism or its toxin. Where possible the hazard characterization should include an indication, for the population of interest, of the probability to cause an adverse health effect as a function of dose; this would ideally take the form a dose-response relationship, if available, or using the *Median Dose* or *Infectious Dose 50 (ID_{50})*, the dose at which 50% of consumers become infected (or ill); see Section 6.3 for details. The hazard characterization may also include identification of different adverse effects for different subpopulations, such as neonates or immunocompromised people. Hazard characterizations can be conducted as stand-alone processes or as component of risk assessment.

A hazard characterization for a particular hazard may serve as a common module or building block for risk assessments conducted for a variety of purposes and in an assortment of commodities. A hazard characterization developed in one country may serve the needs of risk managers in another country when combined with an exposure assessment specific to that country. A hazard characterization developed for one specific food product may be adapted to a food exposure scenario for another food product by taking into consideration the food matrix effects, where possible. In general, hazard characterizations are fairly adaptable between risk assessments for the same pathogen. This is because the human response to infection from a specific pathogen are not considered to be based on geography or culture but are about the interaction between the hazard and the host only, recognising that some hosts will be more susceptible than others.

Hazard characterization, either as part of a risk assessment or as a stand-alone process, can be iterative. For well-established hazards, such as *Campylobacter* or *Listeria monocytogenes*, the hazard characterizations tend to be well developed and may not require much revision unless considerable new information is available. However, for emerging hazards the hazard characterization may be less certain due to lack of data and information, and thus may require more frequently updating to reflect the increasing knowledge about the hazard. These guidelines for the characterization of hazards in food and water follow a structured, step-wise approach, as outlined in Figure 7 and described in detail in subsequent chapters.

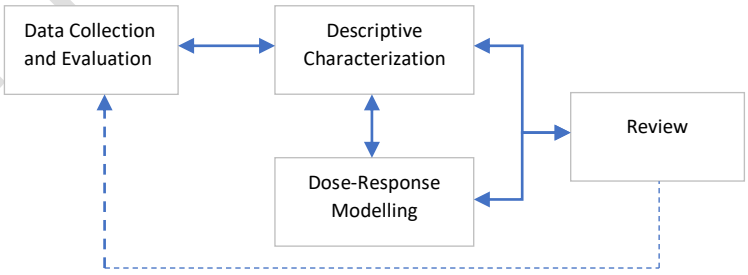


Figure 7: Process flow diagram for hazard characterization of pathogens

6.2 Descriptive Characterization

Descriptive hazard characterization serves to structure and present the available information on the spectrum of human illness associated with a particular hazard, and how this is influenced by the characteristics of the host, the hazard and the matrix, as indicated in Chapter 4. This is based on a qualitative or semi-quantitative analysis of the available evidence and will take the different illness mechanisms into account.

6.2.1 *Information related to the disease process*

When a hazard characterization is being undertaken, one of the initial activities will be to evaluate the weight of evidence for adverse health effects in humans to determine, or confirm, the ability of the hazard to cause disease. The weight of evidence is assessed based on causality inferences appropriately drawn from all available data. This entails examination of the quantity, quality and nature of the results available from clinical, experimental and epidemiological studies; analyses of hazard characteristics; and information on the biological mechanisms involved. When extrapolating from animal or in vitro studies, awareness of the biological mechanisms involved is important with respect to assessment of relevance to humans.

Undertaking hazard characterization for waterborne and foodborne microbial hazards, the biological aspects of the disease process should be considered. Each of these steps is composed of many biological events. Careful attention should be given to the following general points:

- The process as a whole, as well as each of the component steps, will vary by the nature of the hazard.
- Hazards may be grouped in regard to one or more component steps, but this should be done cautiously and transparently.
- The probability of an event at each step may be dependent or independent of other steps.
- The sequence and timing of events are important.

For (toxico-)infectious hazards, it is recommended to consider separately the factors related to infection and those related to illness as a consequence of infection (discussed later, in Section 13.1). While doing so, the following points should be considered when evaluating the available evidence:

- The definition of infection may differ between studies, i.e. is not universally accepted.
- Infection can be measured dichotomously (infection: yes or no), but some aspects can be measured quantitatively.
- Detecting/measuring infection depends on the sensitivity of diagnostic assay.
- Target cells or tissue may be specific (one cell type) or non-specific (many cell types), and local (non-invasive) or invasive or systemic, or a combination.
- The sequence of events and the time required for each may be important and may vary according to the hazard.

The information related to the disease should provide detailed – qualitative or quantitative, or a combination – insights into the disease process. In most cases, this would be based on the available clinical and epidemiological studies. Narrative statements are helpful to summarize the nature of and confidence in the evidence, based on limitations and strengths of the data. Each source of information has its advantages and limitations, but collectively they permit characterization of potential adverse health effects. The analysis should include evaluations of the statistical characteristics of the studies, and appropriate control of possible bias, while identifying what is uncertain and the sources of uncertainty.

Characterization of the adverse human health effects should consider the whole spectrum of possible effects in response to the microbial hazard, including asymptomatic infections and clinical manifestations, whether acute, subacute or chronic (e.g. long-term sequelae), or intermittent (see Table 2). Where clinical manifestations are concerned, the description would include consideration of the diverse clinical forms, together with their severity, which may be variable among strains and among hosts infected with the same strain. Severity may be defined as the degree or extent of clinical disease produced by a microorganism, and may be expressed in a variety of ways, most of

1789 which include consideration of possible outcomes. For mild gastrointestinal symptoms, severity may
1790 be expressed as duration of the illness, or as the proportion of the population affected (morbidity).
1791 Where the gravity of the distress requires medical care or includes long-term illness, or both,
1792 severity may be expressed in terms of the costs to society, such as the proportion of workdays lost
1793 or cost of treatment. Some hazards and the related clinical forms may be associated with a certain
1794 degree of mortality and therefore severity may be expressed as mortality rate (e.g. *Vibrio vulnificus*
1795 infections and *L. monocytogenes* infections). For hazards that cause chronic illness (i.e. the disease
1796 leaves long-term sequelae, e.g. foodborne trematode infections) it may be desirable to include, in
1797 the characterization of the human health effects, considerations related to quality of life as it may be
1798 affected by the disease. Quality of life may be expressed in a variety of ways, depending on the
1799 nature of the illness. For instance, human life expectancy may decrease, chronic debilitation may
1800 occur, or quality of life may be affected by episodic bouts of disease. Increasingly, concepts such as
1801 Quality Adjusted Life Year (QALY) or Disability Adjusted Life Year (DALY), discussed in Section 7.4.2,
1802 are being used to integrate and quantify the effects of different disease end-points on the health of
1803 individuals or populations (Batz, Hoffmann and Morris, 2014; e.g. Havelaar *et al.*, 2000; WHO, 2000,
1804 2015).

1805 1806 *Table 2: Elements that might be included in characterization of adverse human health effects (Adapted from ILSI, 2000)*

Clinical forms
Duration of illness
Severity (morbidity, mortality, sequelae)
Pathophysiology
Epidemiological pattern
Secondary transmission
Quality of life

1807 In addition to a description of the human adverse health effects, information on the disease should
1808 include consideration of the epidemiological pattern and indicate whether the disease may be
1809 sporadic, endemic or epidemic. The frequency or incidence of the disease or its clinical forms, or
1810 both, should be addressed, together with their evolution with time and possible seasonal variations.
1811 The description should include consideration of the repartition of clinical forms according to specific
1812 groups at risk. Finally, the potential for, extent of or amount of transmission, including asymptomatic
1813 carriers, as well as secondary transmission, should also be characterized. Information collected on
1814 these aspects is important to guide the risk characterization phase of the risk assessment.

1815 In all cases, and with particular regard to further modelling, it is important that the characterization
1816 includes a definition of possible end-points to be considered. Thought needs to be given to the
1817 appropriate criteria when defining "infection" of the host by the hazard, and the criteria of what
1818 constitutes a clinical "case". In addition, a definition of the severity scale should be provided,
1819 specifying the indicator chosen (e.g. disease end-point or consequences) and how it can be
1820 measured. The description should also include information on uncertainties and their sources.

1821 To the extent possible, the characterization should incorporate information on the pathophysiology
1822 of the disease, i.e. on the biological mechanisms involved. Depending on the information available,
1823 this would include consideration of elements such as:

1824 - the entrance route(s) of a microorganism into a host;

- the effect of growth conditions on expression of virulence by and survival mechanisms of the microbe;
- the influence of the conditions of ingestion, including matrix effects;
- the influence of gastrointestinal status;
- the mechanisms involved in the penetration of the hazard into tissues and cells;
- the status of the hazard relative to non-specific cell-mediated (innate) immunity;
- the status of the hazard relative to humoral defences;
- the effect of intercurrent illnesses and treatments, such as immunosuppressive or antimicrobial therapy;
- the potential for natural elimination; and
- the behaviour of the hazard in a host and its cells.

The "natural history" of the disease needs to be completed by specific consideration of factors related to the microorganism, the host and the food matrix, insofar as they may affect development of health effects, their frequency and severity.

6.2.2 *Information related to the hazard*

Basically, this information is analysed with a view to determining the characteristics of the hazard that affect its ability to cause disease in the host via transmission in food. The analysis will take the biological nature of the hazard (bacterial, viral, parasitic, prion) into account as well as the relevant mechanisms that cause illness (infectious, toxico-infectious, toxigenic, invasive or not, immune-mediated illness, etc.). In principle, the descriptive hazard characterization is applicable to all types of hazards and all associated illnesses. In practice, by nature of the data collected, the focus will be on acute effects, associated with single exposures rather than long-term effects associated with chronic exposure. Note that the possible interaction between repeated exposures (e.g. the development of acquired immunity) is an integral part of the descriptive characterization.

The ability of a hazard to cause disease is influenced by many factors (Table 3). Some of these factors relate to the intrinsic properties of the hazard, such as phenotypic and genetic characteristics that influence virulence and pathogenicity, and host specificity. The characteristics of the hazard that determine its ability to survive and multiply in food and water, based on its resistance to processing conditions, are critical components of MRA, with reference to both exposure assessment and hazard characterization. Ecology, strain variation, infection mechanisms and potential for secondary transmission may also be considered, depending on the biology of the microorganism and on the context of the hazard characterization, such as the scenario that has been delineated during the problem formulation stage of a full risk assessment.

Table 3: Elements that might be included in characterization of the hazard (Adapted from ILSI, 2000)

Intrinsic properties of the hazard (phenotypic and genetic characteristics)
Virulence and pathogenicity mechanisms
Pathological characteristics and disease caused
Host specificity
Infection mechanisms and portals of entry
Potential for secondary spread
Strain variability
Antimicrobial resistance and its effect on severity of disease

If not already included in the characterization of the hazard, then specific consideration should be given to the intrinsic properties of the hazard that influence infectivity, virulence and pathogenicity; their variability; and the factors that may alter the infectivity, virulence or pathogenicity of the microorganism under consideration. As a minimum, elements to be addressed as best as possible in hazard characterization with regard to the hazard are summarized in Table 3.

6.2.3 *Information related to the host*

Host-related factors are the characteristics of the potentially exposed human population that may influence susceptibility to the particular hazard, taking into account host intrinsic and acquired traits that modify the likelihood of infection or, most importantly, the probability of illness and its severity. Host barriers are multiple in number and pre-existing (innate); they are not all equally effective against hazards. Each barrier component may have a range of effects depending on the hazard, and many factors may influence susceptibility and severity. These are identified in Table 4.

Table 4: Factors related to the host that may influence susceptibility and severity (Adapted from ILSI, 2000)

Age
General health status, stress
Immune status
Underlying conditions, concurrent or recent infections
Genetic background
Use of medications
Pertinent surgical procedures
Pregnancy
Breakdown of physiological barriers
Nutritional status, bodyweight
Demographic, social, and behavioural traits

Not all of the factors listed in Table 4 would be relevant, or important, for all hazards. In all cases, however, an important issue in hazard characterization is to provide information on whom is at risk and on the stratification of the exposed population for relevant factors that influence susceptibility and severity.

6.2.4 *Information related to the matrix*

The factors related to the food matrix are principally those that may influence the survival of the hazard through the hostile environment of the stomach. Such effects may be induced by protection of the hazard against physiological challenges, such as gastric acid or bile salts. These are related to the composition and structure of the matrix (e.g. highly buffered foods; entrapment of bacteria in lipid droplets). Alternatively, the conditions in the matrix may phenotypically affect the ability of the hazard to survive the host barriers, such as increased acid tolerance of bacteria following pre-exposure to moderately acidic conditions, or induction of stress-response by starvation in the environment. Stress conditions encountered during the processing or distribution of food and water may alter a hazard's inherent virulence and its ability to resist the body's defence mechanisms. These potential matrix effects can be important elements in hazard characterization. The conditions of ingestion may also influence survival by altering the contact time between hazards and barriers, e.g. initial rapid transit of liquids in an empty stomach. These factors are summarized in Table 5.

Table 5: Elements that may be included in characterization of the effect of the matrix on the hazard-host relationship.

Protection of the hazard against physiological barriers, e.g. fatty foods, ingestion of pathogen in, or after, ingesting a large volume of fluid
Induction of stress response
Effects on transport of hazard through the gastrointestinal tract

6.2.5 *Relationship between the dose and the response*

The final, and essential, element in the descriptive hazard characterization is the relationship, if any, between the ingested dose, infection and the manifestation and magnitude of health effects in exposed individuals. Specific modelling aspects are covered Sections 6.3 and 11.

Description of the dose-response relationship involves consideration of the elements or factors related to the hazard, the host and the matrix, insofar as they may modulate the response to exposure. Where appropriate information is available, it also involves a discussion about the biological mechanisms involved, in particular whether synergistic action of the hazards, may be a plausible mechanism for any harmful effect, or whether a single hazard may cause adverse effects under certain circumstances. Elements to be considered are listed in Table 6.

Table 6: Elements to be considered in describing the dose-response relationship (Adapted from ILSI, 2000)

Organism type and strain
Route of exposure
Level of exposure (the dose)
Adverse effect considered (the response)
Characteristics of the exposed population
Duration – multiplicity of exposure

Where clinical or epidemiological data are available, discussion of the dose-response relationship will generally be based on such data. However, the quality and quantity of data available will affect the characterization. The strengths and limitations of the different types of data are addressed in Chapter 10. A specific difficulty is obtaining data to characterize infection, or to characterize the translation of infection into illness and illness into different outcomes. In many cases, the analysis may only be able to describe a relationship between a dose and clinical illness. Other difficulties arise from several sources of variability, including variation in virulence and pathogenicity of the microorganisms, variation in attack rates, variation in host susceptibility, and type of vehicle, which modulates the ability of hazards to affect the host. Therefore, it is essential that the dose-response analysis clearly identify what information has been utilized and how the information was obtained. In addition, the variability should be clearly acknowledged and the uncertainties and their sources, such as insufficient experimental data, should be thoroughly described.

In cases where a dose-response model cannot be ascertained or is not really needed, such as a qualitative MRA, an indication of the likely dose required to cause a certain probability of infection/illness should still be considered. In particular, the dose that results in infection/illness in 50% of exposed consumers – often referred to the ID_{50} or median dose – may be a simple, yet practical, indicator. However, such a dose should not be interpreted as a threshold or minimal infective dose (see box below). For example, is the hazard highly infective and only a very small dose is required, as is the case for norovirus, for which it has been estimated that the ID_{50} may be as low as 18 viruses (Teunis *et al.*, 2008). Or is a larger dose required to cause 50% illness, as is the likely

case with *Listeria monocytogenes* in the general population (FAO/WHO, 2004; Buchanan *et al.*, 2017)?

It should be recognised that for many organisms a very low dose may cause illness, even though the probability of this happening may be very low. However, often the exposure distributions (i.e. distribution of doses) are highly right-skewed and so most exposures occur at (very) low doses. As a result, these low doses, together with a small probability of illness may still represent a large number of illnesses in a population; such exposures are consistent with the concept of "sporadic" illness.

6.3 Quantifying the Dose-Response Relationship

Illness can be the result of intoxication, toxico-infections or infection processes. In the first case the illness is the result of ingestion of toxins being preformed in the food. The health risks of certain toxins, e.g. cyanobacterial toxins in water or aflatoxins in foods, usually relate to repeated exposures and hence tend to be chronic; these require another approach, which resembles hazard characterization of chemicals. Other toxins have more acute effects like botulinum toxin, *Staphylococcus aureus* enterotoxin or *Bacillus cereus* cereulide. In toxico-infection organisms produce toxins in the intestines that either produce adverse effects there, or are transported in the body and create effects in other places in the human body, and for infections the organisms invade human cells, being the intestinal cells or for certain pathogens even further into the human body.

To determine the probability of adverse effects, a dose response relation is needed to translate the doses resulting from exposure assessment. For this, a mathematical model is needed, as well as the value(s) of its parameter(s), including variability and uncertainty. Attention should be paid to various aspects:

1. The dose ingested is characterized by the multiplication of the concentration and the amount of food (or water) ingested (that are both variable).
2. The definition of the response(s), e.g. infection, disease, sequelae.
3. The specific model used, e.g. exponential, Beta-Poisson.
4. The set of parameters including variability and uncertainty, potentially relevant for a specific population group and/or food commodity and/or organism subgroup

The Minimal Infective Dose (MID) model posits that there is a dose below which there is no risk, and above which infection always occurs. Microbial dose-response models today are based on the single-hit assumption, i.e. each individual cell has a discrete, non-zero probability of establishing infection. Models based on this assumption can be found in numerous peer-reviewed papers and are also recommended in the WHO/FAO Guidelines for Hazard Characterization of Pathogens in Water and Food (FAO/WHO, 2003). Therefore, the MID concept, the words "minimal infective dose", "infectious dose", or statements like the dose response is between 10^4 and 10^5 cells should not be used. It is appropriate to use an infectious dose for a certain (quantitative) response like ID_{50} or ID_{10}, representing the dose at which 50 or 10% respectively of those exposed get infected. This concept holds true for toxico-infectious and infectious organisms. Sometimes the ID_{50} is used or interpreted as a threshold of infection; however, such an interpretation is incorrect and should be avoided. A minimal toxic dose (MTD) might exist for illness cause by food containing preformed toxins (e.g. staphylococcal enterotoxins), where there is a level below which there is no observable response.

Plots of empirical datasets relating the response of a group of exposed individuals to the dose (often expressed as a logarithm) frequently show a sigmoid shape (e.g. Figure 8 left) and a large number of mathematical functions can be used to model the dose-response relationship (Haas, Rose and Gerba, 2014; Teunis, 1997). It is important to also investigate this curve on log-log basis, since the

'low exposure' (X-axis) and 'low probability' (Y-axis) part of the relationship (Figure 8, right) is often of particular relevance (Williams, Ebel and Vose, 2011a) as explained at the end of Section 6.2.5. It should be noted that the uncertainty bounds appear different in width when viewed on the log-log scale compared with the linear scale. When extrapolating outside the region of observed data, different models may predict widely differing results (Coleman and Marks, 1998; Holcomb *et al.*, 1999). It is therefore necessary to select between the many possible dose-response functions and justify the decision. In setting out to generate a dose-response model, the biological aspects of the hazard-host-matrix interaction should be considered carefully (Teunis, 1997).

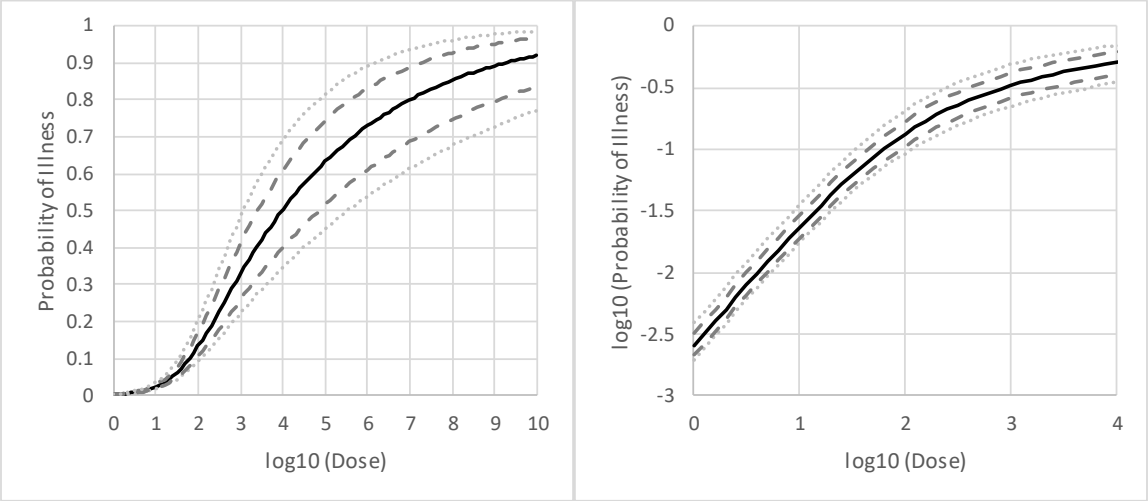


Figure 8: Example Salmonella Dose-Response model, including expected response (solid line), approximate 2.5th and 97.5th uncertainty percentile lines (dashed) and upper and lower uncertainty bounds (dotted) (FAO/WHO, 2002a p. 87) on linear-log scale (left) and on log-log scale (right).

For the use of dose-response models one could use default models and parameter values from other sources (see Table 7). In those cases, relevant assumptions need to be evaluated. It could also be decided to extend the dose-response relation with additional data or derive a fully new dose response model. For deriving new or updated dose response models, guidance is provided in Chapter 13.

Table 7: Dose-response models and parameter estimates commonly used in QMRA.

Organism	Reference	Model	Parameters	Lower bound (Percentile)	Upper bound (Percentile)
Salmonella	FAO/WHO (2002a)	Beta-Poisson	α=0.1324 β=51.43	0.0940 (2.5th) 43.75 (2.5th)	0.1817 (97.5th) 56.39 (97.5th)
Listeria monocytogenes [a]	FAO/WHO (2004)	Exponential (susceptible) Exponential (healthy)	r=1.06×10^{-12} r=2.37×10^{-14}	2.47×10^{-13} (5th) 3.55×10^{-15} (5th)	9.32×10^{-12} (95th) 2.70×10^{-13} (95th)
***Campylobacter* spp.**[b]	FAO/WHO (2009d)	Beta-Poisson	α=0.21 β=59.95		
***Shigella dysenteriae/ E. coli* O157**	Cassin *et al*. (1998)	Beta-binomial	α=0.267 β=Lognormal(5.435, 2.47^2)		
Vibrio vulnificus	FAO/WHO (2005)		α=9.3 × 10^{-6} β=110,000		

[a] For *Listeria monocytogenes*, newer animal model data (Roulo *et al.*, 2014; Smith *et al.*, 2003, 2008; Williams *et al.*, 2007, 2009) and outbreak data (Pouillot *et al.*, 2016) suggest much higher r-values and hence lower ID_{50}s than predicted by this model which was based on the method of Buchanan *et al*. (1997) of matching expected loads of *L. monocytogenes* across the food supply to the total annual cases in a community, and which relies on many untested assumptions.

[b] The dose response relation is for infection and the conditional probability of disease following infection was 33% (29/89) and can be described by a beta(30,61)

7. Risk Characterization

7.1 The Process of Risk Characterization

Codex defines risk characterization as "the process of determining the qualitative and/or quantitative estimation, including attendant uncertainties, of the probability of occurrence and severity of known or potential adverse health effects in a given population based on hazard identification, hazard characterization and exposure assessment." (CAC, 1999). Hence, the risk characterization integrates the findings from those three components (see Figure 2) to estimate levels of risk, which can subsequently be used to make appropriate risk management decisions.

Risk characterization is the final step in the risk assessment component of risk analysis (Figure 2). The risk assessment process is initiated by risk managers who pose specific questions to be answered by the risk assessment. As noted previously, the questions posed by risk managers are usually revised and refined in an iterative process of discovery, discernment and negotiation with risk assessors. Once answered, the risk managers have the best available science-based information they need to support their decision-making process.

Risk characterization is the risk assessment step in which the risk managers' questions are directly addressed. While 'risk characterization' is the process, the result of the process is the 'risk estimate'. The risk characterization can often include one or more estimates of risk, risk descriptions, and evaluations of risk management options. Those estimates may include economic and other evaluations in addition to estimates of risk attributable to the management options.

Although the Codex risk assessment framework is a common context for undertaking risk characterization, it is by no means the only context. In actual practice an assessment of the risk may include some or all of these steps. The scientific analyses comprising any one of these steps may be sufficient on their own for decision-making. Risk assessments can follow a "bottom-up" or "top-down" approach. A bottom-up approach links knowledge about the prevalence and concentration of a hazard in a food source with knowledge about the causal pathways, transmission routes and dose-response relations. Alternatively, top-down approaches use observational epidemiological information to assess risk, typically making use of statistical regression models (Williams, Ebel and Vose, 2011b). Also, models exist that use elements from both approaches, e.g. for source attribution. These approaches have different starting points, use different types of data and serve different purposes. For example, in Denmark (Hald *et al.*, 2004) and USA (Guo *et al.*, 2011), the number of human cases of salmonellosis attributed to different animal sources was estimated without a precise exposure assessment and without using a dose-response model. A further example is provided by De Knegt *et al.* (2015). Bottom up and top down MRA approaches have been published on aiding risk managers in the use of risk metrics (i.e. ALOP, FSO) with case studies using *Listeria monocytogenes* in deli meats (Gkogka *et al.*, 2013a) and *Salmonella* spp. in raw chicken meat (Gkogka *et al.*, 2013b).

7.2 Qualitative Risk Characterization in Risk Assessment

7.2.1 *Introduction*

The risk characterization generated by a qualitative risk assessment, while ideally based in numerical data for exposure assessment and hazard characterization, will generally be of a descriptive or categorical nature that is not directly tied to a more precisely quantified measure of risk. Qualitative risk assessments are commonly used for screening risks to determine whether they merit further investigation and can be useful in the 'preliminary risk management activities' described in (FAO/WHO, 2002b), but may also provide the needed information and analysis to answer specific risk management questions. The major difference between qualitative and quantitative risk

characterization approaches is in the way the information is synthesized and the communication of the conclusions.

7.2.2 *Performing a qualitative risk characterization*

Qualitative risk characterization requires an overall textual estimate of the risk. This may be based upon a combination of the stepwise assessed risks. This is a complex process as it should still obey basic principles of probability theory when combining probabilities but there are no clear rules to the outcome of the combination of (possibly subjective) textual descriptions of probability. For example, Table 8 illustrates a comparison between the process for computing risk estimates in quantitative versus qualitative risk assessments. When combining the equivalent qualitative statements, the only inference that can be made is that the final risk is either of equal magnitude or lower than the probability at the first stage (P1). This qualitative process can lead to errors in probability logic and may be impossible if there is uncertainty to address or multiple pathways to combine (Wooldridge, 2008). Alternatively, Wooldridge (2008) proposes the risk characterization process consist of a summary of the individual conclusions for each of the steps of the risk assessment (including descriptions of uncertainty).

Table 8: A comparison of the process for computing the final risk estimate in risk characterization in quantitative and qualitative risk assessments. (Table adapted from Table 4 in (Wooldridge, 2008)).

Stage	**Quantitative risk assessment**		**Qualitative risk assessment**	
	Probability	**Computation**	**Probability**	**Computation**
P1	0.1		Low	
P2	0.001	*P2* = *P1* x 0.001=0.0001	Very Low	*P1* x Very Low →Very Low or lower
P3	0.5	*P3* = *P2* x 0.5=0.00005	Medium	*P2* x Medium → further reduction
P4	0.9	*P4* = *P3* x 0.9=0.000045	High	*P3* x High→ further (small) reduction
Risk Estimate	**0.000045**		**Very Low or lower**	

Despite its name, a qualitative risk assessment still relies on as much numerical data as possible to provide inputs. The search for information, and thus for numerical data, should be equally as thorough as for a quantitative risk assessment. Also, where there are crucial numerical data deficiencies, expert opinion must again be utilized. The major difference between qualitative and quantitative risk assessment approaches lies in how the data and expert opinion is treated and combined once obtained.

Transparency in reaching conclusions

A qualitative risk characterization should show clearly how each of the risk estimates is reached. The precise way of doing this will vary depending in part on the complexity of the risk assessment, and in part on the risk assessor(s) preferences. Methods used include:

- a tabular format, with data presented in the left-hand column, and the conclusions on risk in the right column; or
- a 'sectional' format with a summary or conclusions section at the end of each data section.

Examples of these formats that illustrate 'good practice' (i.e. documentation of evidence and logic) are presented in Table 9 and Table 10. The examples are based on particular steps in an overall risk

2073 assessment for which the question is: What is the probability of human illness due to microbe 'M', in
2074 country 'C', due to the consumption of meat from livestock species 'S' infected with microbe M?

2075 *Table 9: Example of a possible tabular format for presenting data linked to risk*
2076 *estimates and conclusions.*

Step being estimated: **'What is the probability of a randomly selected example of species S in country C being infected with microbe M?**	
Data available	**Risk estimate and conclusions**
The prevalence of microbe M in species S in Country C was reported as 35% (Smith & Jones, 1999*). The prevalence of microbe M in region R, a district within country C, was reported as 86% (Brown, 2001*). There are no particular geographical or demographic (with respect to S) differences in region R, compared with the rest of C (Atlas of World Geography, 1995*). The diagnostic test for microbe M, used in the livestock surveillance programme in country C is reported to have a sensitivity of 92% and a specificity of 99% (Potter & Porter, 1982*). **Fictional references for illustrative purposes only*	The studies suggest that the probability of a randomly selected example of species S in country C being infected with microbe M is medium to high. However, the two studies indicate that considerable variability by region is likely. With only two studies available, there is also considerable uncertainty of the actual range of prevalence by region, as well as the probability of infection in a randomly selected example of S. In addition, the timing of these surveys may suggest an increasing prevalence of M in C. The reported parameters for the diagnostic test used do not alter these conclusions.

2077 *Table 10: Example of a possible sectional format for presenting data linked to risk*
2078 *estimates and conclusions.*

SECTION X. What is the probability of human ill health, given infection with microbe M?
Data available
• No specific dose-response data has been found for microbe M. • Health authorities for country C provide the following data (National Health Reviews, 1999–2002*).   ○ Incidence over the period was reported as 22 cases per million of the population per year (22 per million is 0.000022% of the population per year). • Clinical incidence recording and reporting systems in Country C are considered to be of exceptionally high quality (Bloggs, pers. comm.*). • Experts' opinions indicate that once clinical symptoms appear, cases are likely to consult a medical practitioner (Journal of Microbial Medicine, 1992*). • Cases tend to be seen in the very young or the very old (Journal of Microbial Medicine, 1992*). • A surveillance study undertaken by practice-based serological testing indicated that 35% of the population of C had been exposed to microbe M and had sero-converted (Hunt, Hunt and Seek, 2001*). This was a countrywide, statistically representational study.

*Fictional references for illustrative purposes only
Conclusions
Data suggest a high level of exposure to microbe M in country C, but a very low incidence of clinical disease. Expert opinion indicates under-reporting of clinical disease due to lack of medical practitioner involvement is unlikely to account for this. Overall, therefore, the probability of human ill health, given infection with microbe M, is likely to be low. The level of uncertainty in the data specific to country C appears to be low, making this conclusion reasonably certain. However, data also indicate that there are specific groups at higher risk of clinical illness, specifically the very old and very young. From the data currently available it is not possible to indicate how much higher this risk is likely to be.

Limitations of qualitative risk characterization

It may be difficult to conceive of a fully qualitative risk assessment that will provide useful advice to risk managers, except in a few special cases. In those special cases, the number of factors that could affect the risk may be very low or every factor that affects the risk, may change the risk in the same direction. Since risk managers may make decisions on the basis of economics, qualitative descriptions may be difficult to translate directly to financial benefits and/or costs. In other cases, it may be virtually impossible to assess the combined effect of multiple stages because the relative contributions of factors, expressed in qualitative terms, cannot be logically combined to determine their overall affect. In some cases, a qualitative best-effort may still be needed, and any assumptions and uncertainties need to be clearly explained. Thus, while a fully qualitative risk assessment can identify pathways or scenarios that lead to extremes of risk, the relative risk from all other scenarios cannot be logically differentiated. Logical qualitative reasoning can provide conclusions like 'the risk of X is logically less than that of Y' where Y is another, more precisely quantified, risk that has previously been deemed acceptable. Such reasoning can also provide conclusions like 'the risk of A is logically greater than that of B' where B is another, more precisely quantified, risk that has previously been deemed unacceptable. One can also argue that both of these approaches are forms of best- and worst-case quantitative risk assessment. Cox, Babayev and Huber (2005) discuss these limitations in greater detail and provide examples.

Qualitative analyses often suffer from the inability to determine what pieces of evidence were influential, how they were combined, and ambiguity concerning the meaning of any assigned risk characterization labels. Without explicit criteria identifying what is meant by descriptions such as high, moderate, and low risk, there is little to distinguish the conclusions from arbitrary and possibly value-laden judgements about the level of risk. These shortcomings tend to make qualitative risk characterization unacceptable in many decision-support situations.

Another limitation of qualitative risk assessment may be to blur the lines between risk assessment and risk management. For example, a risk assessment that concludes the level of the risk under consideration to be 'Low', may be perceived to be making a management evaluation of the risk, and therefore confusing the roles of assessor and manager.

It is possible to present an unstructured analysis as a more structured analysis by including standard documentation headings such as exposure assessment, hazard characterization and risk characterization. Examples that illustrate qualitative approaches that do link evidence and conclusion are presented in Section 8.1.

If the risk assessment will be read by a broader audience, assessors should be mindful that interpretation of words or terms used as descriptors might vary between languages or regions. Even when there is a consensus between assessors and managers over the interpretation of the terms used, some limitations of qualitative risk assessment can be identified.

7.3 Semi - Quantitative Risk Characterization

7.3.1 *Introduction*

Semi-quantitative approaches to risk characterization involve assigning numbers to qualitative estimates in the form of probability ranges, weights or scores, and combining them by addition, multiplication, or other mathematical operation with the objective of achieving a greater level of objectivity compared to qualitative approaches. It is the role of risk characterization to provide to management an unbiased estimate of the level of the risk being considered. Semi-quantitative approaches avoid this problem by using a specific, quantitative meaning (instead of a judgemental meaning) rather than terms like 'Low probability'.

Table 11 and Table 12 provide some example definitions for probability, exposure rate and severity categories where probability ranges have been assigned to qualitative descriptions.

Table 11: Example definitions of probability and exposure frequency categorical labels.

Category	Probability range (Probability of event per year)	Category	Exposures per year
Negligible	Indistinguishable from 0	Negligible	Indistinguishable from 0
Very Low	$< 10^{-4}$, (except 0)	Very Low	1-2
Low	10^{-4} to 10^{-3}	Low	3-10
Medium	10^{-3} to 10^{-2}	Medium	11-20
High	10^{-2} to 10^{-1}	High	21-50
Very High	$> 10^{-1}$ (except 1)	Very High	>50
Certain	1		

Table 12: Example definitions of health effect / severity category labels

Category	Severity description
None	No effect
Very low	Feel ill for few days without diarrhoea
Low	Diarrhoeal illness
Medium	Hospitalization
High	Chronic sequelae
Very high	Death

7.3.2 *Performing a semi-quantitative risk characterization*

Semi-quantitative methods require the development of decision rules guiding how the categorical risk levels are combined and that is logical, aligns with general principles of probability, and is transparent in terms of the operations performed. The options to conduct the risk characterization using semi-quantitative methods spans the continuum between qualitative and quantitative approaches with no single approach endorsed as the single "best" approach in all circumstances. Approaches include (but are not limited to) the combination of labels or scores in algebraic form

with a fixed equation (e.g. specifying multiplication or addition of scores), using specified probability ranges/bounds in place of quantitative point estimates of risk, or using a combinatorial risk-matrix. The level of complexity of the approach varies widely as the exact set of rules to combine the categorical risk levels are often designed specifically for the risk assessment being conducted. Examples of the types of approach that may be used include:

Using an algebraic approach: Components of the risk characterization (and overall risk assessment) are assigned numerical values to represent categorical levels and an equation is specified that defines how the scores or weights are combined. An example using an algebraic approach is RiskRanger by Ross & Sumner (2002). The probabilities involved in exposure and impact are converted to scores from 0 to 1, which are combined (usually by multiplication but including additions, e.g. for recontamination) and subject to logical tests in the software (e.g. to prevent unfeasible risk estimates) to define a "comparative risk" and, in conjunction with the number of consumers, a predicted number of cases of illness is obtained. An example of its use is presented in Section 8.1.7.

Using probability bounds: The categorical labels are assigned probability ranges which are then combined. Often, in the course of carrying out a qualitative risk assessment, one can roughly estimate the probability of exposure, etc., from comparison with other, previously quantified risks or from good data pertaining to the problem in hand. If time or the available data are insufficient to carry out a complete quantitative risk assessment, one can use these categorical labels to express the risk level in a more structured way than a simple description of the evidence one has acquired.

However, when terms like "low risk" or "very low risk" are used, it is very important to consider the number itself, but even more so to examine the context to see what the number means. For example, consider where the probability of botulinum toxin in one can of food from a single supplier is 0.0001. This number itself (0.0001) seems "very low". However, since this number refers to only a single can in a potentially very large population of cans, e.g. 10 million, the resulting number of 'toxic cans' equals 0.0001×10,000,000 = 1,000 cans, which would be considered a very large number of toxic cans, given the nature of the illness. On the other hand, if it is considered a probability of one can per year in the entire world containing botulinum toxin to be 0.01, then this value is 100 times larger than the value above (0.0001), but the actual risk is much lower (i.e. one 'toxic can' in 100 years) – this risk is actually quite low, considering that the yearly worldwide can use is in the trillions rather than millions. Therefore, the denominator of the probability needs to be clearly defined (per serving, per person per year, over the whole population, etc.) and the probabilities need to be considered in this context (risk per serving, for a person per year or for the whole population), to classify them as 'high' or 'low'. In addition, the severity needs to be considered when moving from probability to risk.

For example, if the qualitative risk assessment has determined that:

- the probability a serving could be contaminated is 'Very High',
- the number of servings a random person consumes is 'Medium' and
- the probability of illness given consumption of the contaminated product is 'Low',

one can conclude the composite probability to be between 'Low' and 'Medium' by multiplying the corresponding bounds from each of the probability ranges, as shown in Table 13, using the example definitions from Table 11 and Table 12.

Table 13: Example of combining category labels.

Component	Category	Numerical range
Probability that serving is contaminated	Very High	10^{-1}-1
Number of servings in a year	Medium	10-20
Probability of illness from a contaminated serving	Low	10^{-4}-10^{-3}
Probability of illness in a year	Low to Medium	10^{-4}-2×10^{-2}

This approach enables people to make more consistent, logical conclusions: a 'Low' exposure probability per serving and a 'High' probability of illness given exposure cannot, for example, be categorized as a 'Very High' probability of illness per serving.

It is possible to use categorical labels to perform some rudimentary type of probability manipulation. For example, by carefully defining the ranges assigned to each term, it is possible to combine a 'Low' exposure with a 'High' probability of subsequent health effect (the hazard characterization, or dose-response component) to determine the appropriate categorization for the total risk. It is only possible to maintain consistency and transparency in combining categorical labelling of elements of a risk assessment if numerical ranges have been defined for each label. Combining categorical labelling nonetheless should still be approached with some considerable caution (see Chapter 9).

Using a risk matrix: A risk matrix uses combination rules to combine categorical labels; an example of such a matrix is show in Table 14. This approach has been adopted for many years in other areas of risk assessment but has also received criticism because of the difficulties of defining a robust, defensible treatment of risk characterization (and risk assessment in general). See Levine (2012) and Cox Jr. (2008) for a discussion of these issues and suggestions for improvement.

Table 14: A hypothetical example of a risk matrix to combine likelihood and severity as could be applicable to risk characterization using probability ratings as presented in Table 15.

		A	B	C	D	E
		Negligible	**Minor**	**Moderate**	**Significant**	**Severe**
E	**Very Likely**	Low Med	Medium	Med Hi	High	High
D	**Likely**	Low	Low Med	Medium	Med Hi	High
C	**Possible**	Low	Low Med	Medium	Med Hi	Med Hi
B	**Unlikely**	Low	Low Med	Low Med	Medium	Med Hi
A	**Very Unlikely**	Low	Low	Low Med	Medium	Medium

Table 15: Semi-quantitative allocation of categorical labels to probability ranges.

Probability	Risk Rating
>70%	Very likely
40% to 70%	Likely
10% to 40%	Possible
1% to 10%	Unlikely
<1%	Very Unlikely

Limitations of semi-quantitative risk characterization

Any semi-quantitative risk characterization has limitations which can result in inaccuracies in risk estimates. These are discussed in more detail in Section 9.2.3, and include:

- Number of categories to use: there is no rule regarding the number of categories that should be used, e.g. 5 or 25 categories of severity
- Granularity of scale: a risk whose probability of occurrence falls just above the boundary between two categories, and for which a risk management strategy reduces that probability by a small amount, it could be dropped down one category, but which is indistinguishable from reducing the probability by a factor of 10.
- Difficulty combining probability scores: it is not easy to create a rule with scores that replicates the probability rules.

Data requirements

The basic principle of risk assessment is to collect as much data as possible, providing that the inclusion of more data may affect the decision being made. The data collected for a qualitative risk assessment are often sufficient for semi-quantitative risk assessment needs. The difference between the two is that semi-quantitative risk assessment has a greater focus on attempting to evaluate the components of the risk to within defined quantitative bounds. Thus, at times, one may do a statistical analysis on a data set to attempt to more precisely estimate a probability, or the expected impact, providing it will give the assessor more confidence about how to categorize the risk.

Semi-quantitative risk assessment is usually used as a means to compare several risks or risk management strategies. At times there may be sufficient data to be able to perform a full quantitative risk assessment for a select number of risks (e.g. food–pathogen combinations). A quantitative model can provide more information about specific strategies to apply to that particular risk issue, but the quantitative results can also be used to place these more precisely evaluated risks into context with others of concern in a semi-quantitative environment.

Transparency in reaching conclusions

Semi-quantitative risk assessment is a system for sorting out risks, focusing on the big issues, and managing the entire risk portfolio better. The scoring system is inherently imperfect, but so is any other risk evaluation system. If the scoring system being used can be shown to produce important errors in decision logic, then one can use potentially more precise quantitative risk assessment arguments or change the scoring system to something more precise.

Semi-quantitative risk assessment may offer some advantages in achieving transparency. No sophisticated mathematical model is necessary, for example, which is appealing to the lay person. However, the use of mathematical models as an obstacle to transparency may be overemphasized. Most food safety risk assessments require understanding of complex microbiological information and a reasonable understanding of human medicine and of epidemiological principles, which tend to be postgraduate topics. In contrast, quantitative risk assessment uses mathematics that are generally covered at an undergraduate level. The main obstacle to transparency of quantitative models is that there are only a few people who have specialized in the field.

The key transparency issue with semi-quantitative risk assessment arises from the granularity of the scales used in scoring. The usually rather broad categories mean that lose any distinction between risks which can be considerably different in probability and/or impact magnitude. This means, for example, that one food industry could be unfairly penalized because its product lies just above a category bound, or that industry or regulator only have the incentive to push a risk just over, or below, a category boundary.

7.4 Quantitative Risk Characterization

7.4.1 *Introduction*

As described in Section 5.2.3, quantitative assessment can be either deterministic (where single values, like means or percentiles, are used as model input variables), or probabilistic (stochastic) where probability distributions are the model input variables. Most of the literature, guidance and the best-known examples in QMRA are probabilistic quantitative microbial risk assessments. This approach offers many advantages over deterministic risk assessment, and these are described at length in Chapter 11. Examples of deterministic quantitative risk assessment can be found most readily in the food additive safety assessment (also known as chemical risk assessment) literature. FAO and WHO have produced numerous examples of probabilistic risk assessments, through the Microbiological Risk Assessment Series, as have food safety authorities around the world; some examples are provided in Section 8.2

Quantitative risk characterization addresses risk management questions at a finer level of detail than a qualitative or semi-quantitative risk characterization and facilitates a more precise comparison between risks and between risk management options. This extra level of detail can be at the expense of a far greater time to completion, a reduction in scope and a greater difficulty in understanding the model. Probabilistic techniques are more complex and therefore introduce a greater likelihood of error or misunderstanding. Quantitative risk assessments may also rely on subjective quantitative assumptions (WHO/OECD, 2003), and the mathematical precision of these quantitative results can inadvertently give a false impression of the degree of accuracy in characterizing risk. This has been recognized for a long time in the risk analysis community, e.g. Whittemore (1983) noted: “Quantitative risk analyses produce numbers that, out of context, take on lives of their own, free of qualifiers, caveats and assumptions that created them”.

7.4.2 *Quantitative risk measures*

Quantitative measures of risk must combine the two quantitative components of risk: (a) a measure of the probability/amount of the hazard occurring (i.e. exposure) and (b) the severity of the health effect should that hazard occur (Kaplan and Garrick, 1981).

Measure of exposure

The probability of exposure in microbiological food safety risk assessment must relate to a specified level of exposure, which is the result of the exposure assessment component (Chapter 5). The subsequent probability measures of risk are expressed generally as risk of an outcome (e.g. risk of illness per serving) or as population risk (e.g. risk of the population experiencing more than 10 illnesses per year).

There are advantages and disadvantages in selecting each probability measure. The first option underlines the probabilistic content of the risk measure, while the second can be misread to make one believe that the risk event will occur deterministically with the specified frequency; though explicit identification of the distribution of the risk measure, or associated probability intervals helps to counter that perception.

The choice of probability measure needs to be made carefully and in collaboration with the risk managers, to make any explanation of the risk assessment results as clear as possible to the intended audience.

Measure of health effect

There are different ways of expressing risk (EFSA, 2012). Codex Alimentarius defines risk as “a function of the probability of an adverse health effect and the severity of that effect, consequential

to a hazard(s) in food". There are different metrics that have been developed to characterize and compare risk including the number of an adverse outcome, the Quality-Adjusted Life Year (QALY), the Disability-Adjusted Life Year (DALY) as well as metrics for monetary valuation of public health. Each of these metrics has some pros and cons, and there is no preferred choice for all scenarios. Each individual metric provides a different perspective on the public health risk of foodborne pathogens and the choice should be based on the purpose and scope of the risk assessment. The selected measure(s) of health effect will reflect what the risk manager cares about.

There are many potential adverse health effects that a risk manager might be interested in, in addition to those about which the affected individual is directly concerned. This, in turn, means that there are many possible ways to measure and express the magnitude of the risk (sometimes called the '*risk metric*') that might be selected as the required output from a risk assessment. The selection of a particular measure of risk is therefore not necessarily straightforward, and must be discussed between the risk manager, the risk assessor, and other interested stakeholders. In addition, for quantitative modelling, the unit or units required must be defined whilst considering the practical aspects of modelling so that the outputs can be produced and reported in those units.

A) Number of adverse outcomes: The number of adverse outcomes (e.g. illnesses, hospitalisations, deaths) is the simplest metric that can be used in risk assessment. This number (or the probability) of adverse outcomes can be estimated as "per serving" or "per annum" and standardised for population size (e.g. per 100,000 per year)". In general, the per annum relative risks inherently have a greater degree of uncertainty than the corresponding per serving relative risk because of the additional uncertainty associated with the number of annual servings. Another factor that affects relative risk on a per annum basis is the size of the susceptible subpopulations, in proportion to the total population which are substantially different, e.g. YOPIs (young, old, pregnant, immunocompromised). Note that not all subpopulations may be equally susceptible to all hazards, e.g. susceptibility to infection may differ from susceptibility to microbial toxins produced in the food prior to consumption.

- **Risk of some outcome per serving**: requires that a serving be defined (e.g. 100 g of cooked chicken, 150 ml of orange juice, or use of a serving size probability distribution). The risk of some outcome per serving measure provides an easy comparison of the risk from direct consumption of different food products. It can also be helpful in establishing cost-benefit type arguments where, for example, one is looking for the lowest risk for a given nutrition requirement.
- **Individual risk**: can be specified for a random individual within the population of concern, or for a random consumer of the product. If a random consumer of the product is assumed this presupposes that there are no significant secondary infections or cross-contamination effects. Random individuals can be assumed to be part of various subpopulations if one wishes to explore the risk to different subpopulations. Examples of different individual risk estimates include:
    i. The probability per year that a random individual will suffer illness X from exposure to bacteria Y in food Z;
    ii. The probability per year that a random individual will suffer any deterioration in health X from exposure to bacteria Y in food type Z;
    iii. The probability that a person will suffer some adverse health effect in their lifetime from exposure to bacteria Y in foods;
    iv. The expected number of foodborne-related adverse health events for a random individual from consuming food type Z in a year;

v. The distribution of the number of foodborne-related adverse health events for a random individual from consuming food type Z in a year;
vi. The per capita (or per kg consumed, or per kg produced, by the nation) expected incidence of health impact X from food type Z.

This risk per person is very often a very low number (e.g. 0.000013 expected illnesses per person per year), making it difficult to understand and compare. These values can be made more useable by considering the risk over a large number of people (e.g. 1.3 expected illnesses per 100,000 people per year).

- **Population-level risk**: this estimation considers the risk distributed over the population or subpopulation of interest and might also look at the risk burden to the whole population. It may not distinguish between subgroups within that population, such as by region, ethnicity, age or health status. The following are some examples of population-level risk estimates:
  i. Uncertainty about the total expected number of cases of foodborne illness within the population in a year;
  ii. Expected number of hospital bed-days taken up per year as a result of a particular foodborne pathogen;
  iii. Probability that there will be at least one outbreak (or one death, one illness, etc.) in the population in a year;
  iv. Probability that there will be more than 10,000 illnesses in the population in a year.

  These estimates can be produced for separate subpopulations if required and aggregated to a single measure for the whole population.

B) Health adjusted life years (Burden of disease). Summary measures of public health can characterize and compare the health effect of diverse risks and health outcomes. These are particularly useful when a risk assessment is considering or comparing different pathogens. For example, deciding between risk management options that pertain to two different pathogens requires a method that accounts for the differences in severity between those pathogens. In contrast, if a risk assessment is concerned with a particular product-hazard pairing, and the severity of outcomes is independent of exposure pathway, then these summary metrics are less critical. For example, deciding between risk management options that pertain to controlling illnesses for a particular product-hazard pair is less dependent on the differences in severity between the options (because this is the same).

Different methods have been developed that provide a common metric for more fully valuing and comparing health risks. Health-adjusted life years (HALYs) are non-monetary health indices and are summary measures of population health permitting morbidity and mortality to be simultaneously described within a single number (Gold, Stevenson and Fryback, 2002). HALYs are used in economic cost-effectiveness analyses, also sometimes referred in the literature as cost-utility analysis or weighted cost-effectiveness analysis (Mangen *et al.*, 2010). The two most prominent HALYs are Quality-Adjusted Life Years (QALYs) and Disability Adjusted Life Years (DALYs).

The DALY is based on the amount of life quality lost multiplied by the duration of that health state (Van der Fels-Klerx *et al.*, 2018). They are useful for overall estimates of burden of disease, comparisons of the relative impact of specific illnesses and conditions on communities, and in economic analyses. The DALY method presumes perfect health for the entire life span, and therefore measures the loss due to ill health. The QALY concept is analogous, but measures the increase in quality of life, and its duration, as a result of an actual or putative intervention.

The DALY approach has been used by WHO to quantify the global burden of foodborne disease as it incorporates life years lost through specific types of disability, pain or other reduced quality of life, including premature mortality. This allows the comparison of one health state with another, and with mortality itself. Integrated health measures provide information to put diverse risks into context. The WHO Initiative to Estimate the Global Burden of Foodborne Diseases (WHO, 2015) provides an estimation of global foodborne disease incidence, mortality, and disease burden in terms of DALYs for thirty-one foodborne hazards (including 11 diarrhoeal disease agents, 7 invasive infectious disease agents, 10 helminths and 3 chemicals).

DALYs lost is the summation of two quantities:

1. YLL: Years of life lost (the difference between the age at death and the life expectancy)

2. YLD: Years lived with a disability (multiplied by the extent of the disability)

Given values of these disability rates, and data on time course (distribution) of severity of outcomes, the DALYs in units of total years of impact in the population under consideration can be computed (Ssemanda *et al.*, 2018). This formulation recognizes that different illnesses will have different patterns of severity and longevity of disability (Haas, Rose and Gerba, 2014). The DALY methodology has been widely used in both national (Lake *et al.*, 2010; Monge *et al.*, 2019; Scallan *et al.*, 2015; Ssemanda *et al.*, 2018) and global (Mangen *et al.*, 2010) disease burden estimations or to compare the burden of disease estimates attributed to different cooking practices (Berjia, Poulsen and Nauta, 2014).

A related approach to integrate the spectrum of health outcomes is the QALY (quality adjusted life year) approach. QALYs differ from DALYs primarily by the nature of the weights used. Rather than using expert-derived “disability weights,” the QALY concept uses “quality weights” which are based on survey or preference data to assess the relative perceived quality of life under certain health impairments. Such an approach allows for the differentiation among subpopulations, socioeconomic conditions, and differences in underlying society (Haas, Rose and Gerba, 2014).

The DALY method is considered by some to be preferable to the QALY method for making societal resource allocation decisions. The QALY method was intended to evaluate the benefit in quality of life improvement through a medical intervention, i.e. compared to the cost, while DALY mostly seeks to quantify the burden of disease due to a particular hazard in a particular context.

A strong point of the HALY approach is that utilities and disability weights are not income constrained. However, HALYs do not capture non-health effects and HALY impacts cannot be compared to other non-health projects (as would be the case if all effects would be expressed in monetary values). HALYs are based upon the assumption that a life-year is the appropriate metric for measuring health; as a result, the valuation of permanent disability and mortality is linearly valued by age of patients. DALYs and QALYs are semi-quantitative estimates based on disability scoring, and their accuracy is highly dependent on the quality of input data and risk assessment models used for estimating the incidences of relevant health outcomes (Van der Fels-Klerx *et al.*, 2018).

C) Monetary risk metrics. The public health impact of foodborne disease can also be characterized using monetary metrics (Mangen *et al.*, 2010). However, health economics is a branch of economics with additional complexities (Arrow, 1963). Factors that distinguish health economics from other areas include extensive government interventions, uncertainty in several dimensions, asymmetric information (the physicians know more than the patients), barriers to entry, externalities

(communicable diseases, fear of catching disease) and the presence of a third-party agent (professional health care provider).

Several different approaches have been developed for the monetary valuation of risk (Mangen *et al.*, 2010). There are three general approaches:

(1) the human capital approach, measuring a person´s production in the marketplace;
(2) cost of illness (COI) methods, and
(3) revealed or stated preferences which also include intangibles (not measurable) factors such as suffering and pain.

With the human capital approach, the benefits of a health program or costs of disease is measured by the impact on a person's productive input. The human capital approach is generally restricted to the impacts on labour productivity (e.g. foregone income) and makes no attempt to include intangible costs. It is therefore not considered a measure of individual or social welfare. Opportunity costs of time or a replacement cost approach are two methods usually used to value the time for non-market activities (e.g. home-keeping).

A second approach to measuring the public health impact of disease is the cost of illness (COI) method. The COI approach does not measure intangible costs but traces the economic flow associated with an adverse health outcome through the quantification of measurable monetary costs. Cost-of-illness (COI) measures include (Mangen *et al.*, 2015):

1) the costs related to the resources used within the healthcare sector;
2) the resources used by patients and their families; and
3) productivity losses and other non-healthcare related resources used that are indirectly related to illness (e.g. special education).

The COI method estimates the money spent on medical expenditures and the value of the productivity of the patient foregone as a result of foodborne illnesses, complications and deaths. It can be applied wherever there are quantitative data relating to the impact of disease and sufficient cost data for calculating resultant treatment costs and loss of income. Subject to data availability, it is possible to compare large numbers of food risks using COI (Van der Fels-Klerx *et al.*, 2018). COI can be applied for comparing diseases (Mangen *et al.*, 2015), for food-disease combinations (Thomsen *et al.*, 2019), for supply chain analysis of a single food-disease combination (Duncan, 2014; McLinden *et al.*, 2014; Monge *et al.*, 2019), and for comparing the cost-effectiveness of different interventions to reduce the foodborne risk (Lawson *et al.*, 2009).

A third approach uses stated preference studies that are based on the presentation of hypothetical scenarios on which to evaluate how much a person would pay for reductions in the risk of death or other adverse health states. Stated preventative studies can be designed for a specific health state, but are based on a hypothetical construction and, therefore, describe the intention of individuals to adopt particular decisions (Mangen *et al.*, 2010).

Matching dose-response endpoints to the risk measure

Exposure to microbiological agents can result in a continuum of responses ranging from asymptomatic carriage to death. Risk characterization needs to consider the reported health outcome used in developing the dose-response relationship and may require estimating the desired risk assessment endpoint(s) from a more or less severe measurement endpoint. A fraction of exposed individuals will become infected. Infection may be measured as the multiplication of organisms within the host, followed by excretion, or a rise in serum antibodies. A fraction of those

infected will exhibit symptomatic illness, known as the *morbidity ratio* (Haas, Rose and Gerba, 2014), as measured by clinical observation or reported by patients or consumer responses. A fraction of those becoming ill will suffer severe symptoms (e.g. bloody diarrhoea), require medical care or hospitalization, or will die, known as the *mortality ratio* or *case-fatality rate* (Haas, Rose and Gerba, 2014). It should also be noted that DALY and QALY are not typically dose-response endpoints; rather, the endpoints are infections, illness, death. A template (e.g. DALY/case) must be used to translate the risk estimate (e.g. cases) from a quantitative microbial risk assessment to DALYs, etc.

In addition, care must be taken to ensure that the implications of the case definition used in a clinical trial or epidemiological investigation are understood. For clinical trials, typical measurement endpoints include infection (e.g. as indicated by a faecal positive) or illness (e.g. as indicated by diarrhoea). Epidemiological surveys may provide information on morbidity and mortality ratios. These ratios might be dose-dependent, but epidemiological data may not indicate this relationship. In some cases, clinical trials have used a continuous dose-response measurement endpoint (e.g. volume of diarrhoea excreted) that might provide some insight about the dose-dependency of outcome severity (Coleman *et al.*, 2004).

Accounting for subpopulations

Subpopulations may vary with respect to susceptibility, exposure, or both. If the risk characterization seeks to distinguish risk by subpopulation (e.g. by age class), then the exposure assessment outputs should be kept separate for each subpopulation to reflect variation in exposure among them (e.g. the frequency, size and preparation of servings consumed by members of each age class). Even where separate dose-response relationship by subpopulation cannot be specified, it may be informative to characterize risk by subpopulation.

The subpopulations of interest to the risk managers (e.g. susceptible consumers) may not correspond directly to easily identified categories (e.g. age classes). There should be a reasoned basis for classifying consumers as members of different subpopulations, and that subpopulation definitions are consistent between the exposure and dose-response analyses.

7.4.3 *Integration of hazard characterization and exposure assessment*

Codex guidelines describe the need to assess exposure to a hazard and assess the level of risk (dose-response relationship) that the exposure represents. Most quantitative risk assessments will implement the exposure and dose-response models separately, and risk characterization will connect these to estimate the risk. This need for connection should be included in the planning stage of the modelling whenever possible, to avoid having to adjust the output of exposure or the input of the dose response to achieve consistency.

When there is a logical separation between variability and uncertainty in either the exposure assessment or hazard characterization, this distinction should be propagated through the process of integration to determine both the variability and uncertainty in the relevant measures of risks that are the focus of the assessment. Failure to maintain separation between variability and uncertainty can profoundly affect the risk characterization (Nauta, 2000). Additionally, assumptions implicit to specific dose-response models or potential biases associated with estimation of the dose-response can limit how exposure and dose-response can be combined.

In the section below the dose concepts as formulated above are briefly reviewed and suggestions are offered to address the issues of maintaining consistency of units, dose-response model rationales and reducing biases when integrating potentially inconsistent exposure and hazard characterizations.

Units of dose in exposure assessment

According to Codex (CAC, 1999) the output of the exposure assessment is defined as an estimate, with associated uncertainty, of the likelihood and level of a pathogen in a specified consumer portion of food. This exposure estimate is commonly represented by a distribution of the probability that a randomly selected portion of food is contaminated with the pathogen, combined with a probability distribution representing the numbers (or concentration) of pathogens in those portions of food that are contaminated (i.e. contain one or more cells of the pathogen).

Whether the level of contamination is expressed as a concentration (CFU per gram or per ml) or a number (CFU) is important when linking this exposure output to a dose-response model. Numbers of CFU potentially ingested are necessarily positive integers, so a discrete distribution may be the most natural choice for the estimated exposure. The use of a continuous distribution for modelling of individual exposures would be most appropriate when pathogen concentrations are relatively high but can always be converted back to a discrete distribution with some rounding function. Continuous distributions are often used for bacterial counts because they are more flexible and easier to manipulate than discrete distributions. If a concentration is used to express the level of exposure, the concentration has to be multiplied by the amount of food ingested to determine the individual exposure. If the concentration being modelled is in the form of a probabilistic mean, then one needs to use dose-response functions for which inputs are probabilistic (usually, Poisson) mean doses rather than dose-response functions whose input is an actual dose (Haas, 2002; Pouillot, Chen and Hoelzer, 2015).

Units of dose in dose-response assessment

Dose-response models in microbiological risk assessment typically apply the concepts of non-threshold mechanisms, independent action and the particulate nature of the inoculum (Chapter 11). This results in the application of single-hit models like the exponential model, the Beta-Poisson model, the Weibull-Gamma model and the hypergeometric model (Haas, 1983; Teunis and Havelaar, 2000). These models assume each ingested cell acts independently, and all cells have the same probability of causing infection. The non-threshold assumption implies the existence of some level of risk for any dose greater than zero.

A review of dose-response models is provided Chapter 11. The two principle types of data useful for developing a dose-response assessment are clinical feeding trial studies with human volunteers and epidemiological outbreak data and data on disease incidence associated with foodborne exposure. These different types of human data have varying strengths and weaknesses, as discussed in Chapter 10.

Combining exposure and dose-response assessments

Consistency is important when combining exposure and dose-response assessments. The exposure assessment and hazard characterization should be applicable to the same hazard and the same population (e.g. one might mistakenly use a dose-response relationship estimated using data from young healthy volunteers to a less homogenous population that includes susceptible individuals). Such extrapolations should be avoided by looking at alternative modelling approaches. However, if extrapolation is done, then it should be clearly stated, and the potential biases and uncertainties of such extrapolation should be incorporated as part of the assessment.

The output of the exposure assessment should be in units of ingested organisms (CFU, cells, virus particles, etc.) per individual and usually on a per-exposure event basis. In contrast, the input of the dose-response may not be on a per-individual level. For example, the exposure may be expressed as

a mean or other summary of a distribution of exposures over a group of individuals (e.g. Teunis *et al.*, 2010), though this should be avoided if at all possible. Differences between individual- and group-level exposure summaries in a hazard characterization may create problems of consistency when combining the two assessments for the purpose of risk characterization.

Exposure assessment and hazard characterization can be combined in a Monte Carlo simulation by calculating a probability of infection (or illness) associated with each sample from the exposure distribution. For a given sample containing a known number of cells from the exposure distribution, the probability of infection from the specified dose, would then be calculated based on the dose-response relationship. Exposure and risk predictions will generally be uncertain due to the uncertainty associated with alternative models of the exposure distribution and the risk of illness at any specified dose level. These uncertainties extend to predictions of risk when the exposure and dose-response are combined and should be properly represented in the output of the assessment.

Limitations of quantitative risk characterization

Just as with qualitative and semi quantitative risk characterization, there are limitations of quantitative risk characterization as well. These primarily stem from its advantages and are related to the potential need for large quantities of data, as well as the use of complex models. Because of the data and modelling needs, some multi-disciplinary teams tasked with performing quantitative risk characterization can be quite large, and thus costly and time-consuming. The complex nature of the models often makes the review of such models limited to select experts, as well as time consuming. This complexity can also provide a challenge to transparency as complex models may not be easily interpreted by non-experts.

8. Examples

The examples below are provided to give a perspective on the breadth and depth of published risk assessments. Some were done at the country level, others in larger or smaller regions. Some were done in the early days of risk assessment and others more recently. Some were done by federal employees, while other were done in partnership with academic experts. Some focus on a particular food, while others focus on large food categories. Some are for a single pathogen, while others focus on two or more. Some are "farm to fork" while others focus on a specific part of the food chain. Most focus on infectious pathogens, but one focuses on a toxin(histamine) produced by microbial action. Some of the examples are qualitative, others semi-quantitative (Section 8.1), while others are quantitative (Section 8.2).

8.1 Examples of qualitative – semi-quantitative risk assessments

8.1.1 *Risk assessment for main determinants of antibiotic resistance in South East Asia*

The emergence of antibiotic resistant bacteria and genes has been observed in the environment, driven by the indiscriminate use of antibiotics in human and veterinary medicine and food production. A qualitative risk assessment was conducted to evaluate the relative effects of the main determinants of antibiotic resistance, and to estimate the risk of the emergence and spread of antibiotic resistance among humans in the WHO South East Asia region (Chereau *et al.*, 2017). Factors were examined at the policy level (e.g. scope of policies and guidelines), system level (e.g. implementation of healthcare, wastewater, or agriculture and livestock management options), and at individual level (e.g. human behaviour).

The region considered includes 11 countries (Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand, and Timor-Leste).

Hazard Identification: Seven bacteria with high levels of antibiotic resistance were identified and the study focused on those causing infections with high mortality (extended spectrum β-lactamase and carbapenemase producing Enterobacteriaceae and meticillin resistant *Staphylococcus aureus* (MRSA).

Exposure Assessment: the process leading to the acquisition, selection, and spread of the resistant bacteria and genes in humans was described, including the reservoirs, transmission routes, and biological determinants of the emergence and transmission of resistance. Exposure routes considered included the release from human and animal waste, aquaculture, and pharmaceutical industry, ingestion of contaminated food and water, direct contact with reservoirs (animals, soil, water), and human-to-human transmission (including health case workers).

A context assessment was also conducted which looks at the environment in which the event is taking place considering socioeconomic, ecological, other factors that may affect the exposure and/or risk.

Risk Characterization: the likelihood of occurrence of each event was rated using a qualitative approach using:

- *Negligible*: the event occurs under exceptional circumstances
- *Low*: the event occurs some of the time
- *Moderate*: the event occurs regularly
- *High*: the event occurs in most circumstances.

The events in the chain were chronologically integrated leading to transmission of antibiotic resistance in the human population using a matrix to calculate the risks from two consecutive, and dependant events. When multiple independent events contributed to the estimation of risk, the highest risk was used. The risk matrix used was from Wieland *et al.*, (2011), and is designed to combine two risk estimates based on the assumption that the second event is fully conditional on the previous event, and is shown in Table 16.

The risk assessment concluded that South East Asia is at high risk of the emergence and spread of antibiotic resistance in humans. The assessment provides an overall picture of the factors affecting the emergence of antibiotic resistance emergence in humans in the WHO South East Asia Region, and highlights the limited benefit of interventions that are sector specific as opposed to an overall holistic 'One Health' approach.

Table 16: Risk matrix used to combine two consecutive, and dependant events (adapted from Wieland et al., 2011)

Event 2 / Event 1	Negligible	Low	Moderate	High
Negligible	Negligible	Negligible	Negligible	Negligible
Low	Negligible	Low	Low	Low
Moderate	Low	Low	Moderate	Moderate
High	Low	Moderate	Moderate	High

8.1.2 *Faecal pollution and water quality, WHO*

The 'Annapolis Protocol' (WHO, 1999) was developed in response to concerns regarding the adequacy and effectiveness of approaches to monitoring and management of faecal-polluted recreational waters. One of the most important changes recommended in the Annapolis Protocol was a move away from sole reliance on 'guideline' values of faecal indicator bacteria to the use of a qualitative ranking of faecal loading in recreational-water environments. The protocol was tested in several countries, and an expert consultation was convened by WHO. A revised Chapter 4 in Volume 1 of the guidelines was produced from the expert consultation, which described a suitable approach to risk assessment and risk management (WHO, 2003). Tables were produced for water bodies affected by three different sources of human faecal contamination: sewage outfalls, riverine discharges and bather shedding. The tables were based on qualitative assessment of risk of exposure under 'normal' conditions of sewage operation, water levels, etc, and classified the potential human risk. Table 17 reproduces the classification for sewage outfalls.

Table 17: Relative risk potential to human health through exposure to sewage through outfalls (reproduced from WHO, 2003).

		Discharge type	
Treatment	**Directly on beach**	**Short outfall[a]**	**Effective outfall[b]**
None[c]	Very High	High	NA[d]
Preliminary	Very High	High	Low
Primary (including septic tank)	Very High	High	Low
Secondary	High	High	Low
Secondary plus disinfection[e]	Moderate	Moderate	Very Low
Tertiary	Moderate	Moderate	Very Low
Tertiary plus disinfection	Very Low	Very Low	Very Low
Lagoons	High	High	Low

Notes: (a) The relative risk is modified by population size. Relative risk is increased for discharges from large populations and decreased for discharges from small populations. (b) This assumes that the design capacity has not been exceeded and that climatic and oceanic extreme

conditions are considered in the design objective (i.e. no sewage on the beach zone). (c) Includes combined sewer overflows. (d) NA = not applicable. (e) Additional investigations recommended to account for the likely lack of prediction with faecal index organisms

8.1.3 *Drinking Water Guidelines, Australian National Health and Medical Research Council*

As part of Australia's National Water Quality Management Strategy the Australian National Health and Medical Research Council produced the Australian Drinking Water Guidelines (NHMRC, 2018) as a framework for good management of drinking water supplies. The guidelines are not mandatory standards but are designed to provide an authoritative reference document and framework for good management of drinking water supplies to assure safety at point of use by consumers in all parts of Australia. The guidelines consider that the greatest risks to consumers of drinking water are pathogenic microorganisms, and as such covers similar issues for water that microbiological food safety risk assessment covers for food. However, it should be noted that the issues of microbiological growth and inactivation are likely to play a much larger role in microbiological food safety risk assessment because of the greater potential for microbial growth in foods, and the application of strong inactivation processes that do not occur in water in nature. The extensive guidelines document includes a qualitative method for assessing human health risks and recommends that risks should be assessed at two levels:

- **Maximum risk** in the absence of preventive measures; and
- **Residual risk** after consideration of existing preventive measures.

The level of risk of each hazard (pathogen, or hazardous event) is qualitatively assessed by combining a qualitative assessment of the likelihood of the hazard occurring, and the severity of the consequences if it were to occur, according to Table 18,Table 19 and Table 20 (Tables 3.1, 3.2 and 3.3 in the original document), which were developed from the Australian/New Zealand risk analysis standard 'AS/NZS 4360:1999 Risk management', which has since been superseded by AZ/NZS ISO 31000. The guidelines document also includes what are essentially qualitative hazard identification and hazard characterizations for a wide range of water-borne hazards that can be used to assist in the application of the risk matrices. The stated aim of the methodology is "to distinguish between very high and low risks" (NHMRC, 2018).

Table 18: Qualitative measures of likelihood.

Level	Descriptor	Example description
A	Almost certain	Is expected to occur in most circumstances
B	Likely	Will probably occur in most circumstances
C	Possible	Might occur or should occur at some time
D	Unlikely	Could occur at some time
E	Rare	May occur only in exceptional circumstances

Table 19: Qualitative measures of consequence or impact.

Level	Descriptor	Example description
1	Insignificant	Insignificant impact; little disruption to normal operation; low increase in normal operation costs
2	Minor	Minor impact for small population; some manageable operation disruption; some increase in operating costs
3	Moderate	Minor impact for large population; significant modification to normal operation but manageable; operation costs increased; increased monitoring

4	Major	Major impact for small population; systems significantly compromised and abnormal operation, if at all; high level of monitoring required
5	Catastrophic	Major impact for large population; complete failure of systems

Table 20: Qualitative risk analysis matrix: level of risk.

	Consequences				
Likelihood	1 Insignificant	2 Minor	3 Moderate	4 Major	5 Catastrophic
A (almost certain)	Moderate	High	Very high	Very high	Very high
B (likely)	Moderate	High	High	Very high	Very high
C (possible)	Low	Moderate	High	Very high	Very high
D (unlikely)	Low	Low	Moderate	High	Very high
E (rare)	Low	Low	Moderate	High	High

8.1.4 *BSE/TSE risk assessment of goat milk and milk-derived products, EFSA*

A research group in France found a suspected case of Bovine Spongiform Encephalopathy (BSE) infection in a slaughtered goat in 2002. As a result, the European Commission (EC) requested advice from the European Food Safety Authority (EFSA) on the safety of milk and meat in relation to Transmissible Spongiform Encephalopathy (TSE) in goats and sheep. EFSA (2004a) published the following preliminary statement:

> *"From the limited data available today it is concluded that in the light of current scientific knowledge and irrespective of their geographical origin, milk and milk derivatives (e.g. lactoferrin, lactose) from small ruminants **are unlikely to present any risk** of TSE contamination provided that milk is sourced from clinically healthy animals. Exclusion of animals with mastitis is considered to reduce the potential risk. Further assurance of healthy milk could include milk tests for total somatic cell counts indicative of inflammation." [Emphasis added].*

EFSA also commented in a press release:

> *"A comprehensive and quantitative assessment of the risks involved in the consumption of goat meat, milk and dairy products will only be possible if more scientific research data on the occurrence of TSE in small ruminants can be obtained. Such a quantitative risk assessment, if feasible, will take considerably more time."*

It is extremely difficult to assess the risk of BSE-contaminated product because there is no means to measure the number of prions present in a food product, and no human dose-response relationship for prion levels. EFSA nonetheless needed to provide comment on the level of the above risk and relied on an expert panel to review the available data.

8.1.5 *Geographical BSE cattle risk assessment, EFSA*

In 2003, EFSA was requested by the European Commission (EC) to re-assess geographical BSE risk (GBR) and concluded the following (EFSA, 2004b):

> *"The Geographical BSE-Risk (GBR) is a qualitative indicator of the likelihood of the presence of one or more cattle being infected with BSE, pre-clinically as well as clinically, at a given point in time, in a country. Where its presence is confirmed, the GBR gives an indication of the level of infection.*

The GBR assessments are based on information submitted by countries concerned in response to a European Commission recommendation in 1998 setting out the information requirements for such an assessment. The information concerns in particular imports of bovines and meat and bone meal (MBM) from the United Kingdom and other BSE-risk countries, rendering standards for animal by-products, use of so called Specified Risk Materials (SRMs), feeding of MBM to ruminants, etcetera.

Table 3.5 [Table 21] shows the current GBR levels of the seven countries assessed by EFSA so far, as well as their former classification where available."

Table 21: Geographical BSE Risk (GBR) in 2003 in seven countries as assessed by EFSA (2004b; Table 3.5). Earlier assessed levels are also shown.

GBR level	Presence of one or more cattle clinically or preclinically infected with the BSE agent in a geographical region or country	GBR of the country or region Current status (status before)
I	Highly unlikely	Australia (I)
II	Unlikely but not excluded	Norway (I), Sweden (II)
III	Likely but not confirmed or confirmed at a lower level	Canada (II), Mexico (N/A), South Africa (N/A), USA (II)
IV	Confirmed at a higher level	none

NOTES: N/A = not applicable, i.e. not assessed before"

8.1.6 *Risk profile of Mycobacterium bovis in milk, New Zealand Food Safety Authority*

The New Zealand Food Safety Authority commissioned the New Zealand Institute of Environmental Science & Research Ltd (ESR) to provide a 'Risk profile' of *Mycobacterium bovis* in milk (Lake *et al.*, 2009).

The analysis took the form of a 'Risk Profile' which is used in the New Zealand food safety system to rank food safety issues for risk management. It forms an early part of their risk evaluation process, which comprises:

- identification of the food safety issue;
- establishment of a risk profile;
- ranking of the food safety issue for risk management;
- establishment of risk assessment policy;
- commissioning of a risk assessment; and
- consideration of the results of risk assessment.

The pathogen was selected for assessment because

"although it is likely to have minimal public health significance, demonstration of the safety of New Zealand produced food with respect to this pathogen may have trade implications. The food most commonly associated with transmission to humans is cow's milk."

The system for assignment of a category for a food/hazard combination uses two criteria: incidence (rate) and severity assigning categories to the estimate of each. A four-category scoring system was proposed for the rate (see Table 22), based on foodborne disease rates experienced in New Zealand (Lake *et al.*, 2005). Note that this is a generic scoring system that would be adapted to *Mycobacterium bovis* in milk.

A three-category scoring system was proposed for the severity (see Table 23), based on a comparison of the proportion of New Zealand foodborne cases that result in severe outcomes (long-term illness or death) (Lake *et al.*, 2005). Note that this is a generic scoring system that would be adapted to *Mycobacterium bovis* in milk.

Table 22: The four generic categories proposed in New Zealand for the incidence (rate) with examples (Appendix 1 in Lake et al., 2005).

Rate Category	Rate range (per 100 000 per year)	Examples of food hazard combinations
1	>100	Significant contributor to foodborne campylobacteriosis
2	10–100	Major contributor to foodborne salmonellosis Significant contributor to foodborne noroviruses
3	1–10	Major contributor to foodborne yersiniosis, shigellosis
4	<1	Major contributor to foodborne listeriosis

Table 23: The three generic categories proposed in New Zealand for severity with examples (Appendix 1 in Lake et al., 2005).

Severity Category	**Fraction of cases that experience severe outcomes**	**Examples**
1	5%	Listeriosis; STEC; hepatitis A; typhoid
2	0.5-5%	Salmonellosis; shigellosis
3	<0.5%	Campylobacteriosis; yersiniosis; noroviruses; toxins

Analysis for *Mycobacterium bovis* in milk was hampered by a complete lack of prevalence information, so it was considered impossible to make even qualitative statements of exposure. The only available dose-response data were from animal experiments from 1934 and earlier, making it meaningless to consider a usual food safety risk assessment of exposure and hazard characterization. The risk profile method is based solely on epidemiological data in an attempt to inform decision-makers of how important the issue is among other food safety issues that need to be managed. The analysis discussed the available evidence and gave the following scores:

- **Severity**: 1 (>5% serious outcomes)
- **Incidence**: 4 (<1 per 100 000 people per year)
- **Trade importance**: high

Note that the risk assessment titles described these as 'qualitative' risk assessments. However, the numerical definitions of the broad category bands would place these risk assessments within the range of semi-quantitative risk assessments as discussed in this document.

8.1.7 *Seafood safety using RiskRanger, Australia*

Sumner *et al.* (2004) discuss the continuum between qualitative and quantitative risk assessment for seafood, and introduce a semi-quantitative risk assessment method that has been coded into a decision support software tool called RiskRanger (Ross and Sumner, 2002; Sumner and Ross, 2002),

which is freely-available[10]. The tool requires answers to 11 questions, which describe the factors throughout the food chain that affect the food safety risk. The questions can be answered in either qualitative (with predetermined categories) or quantitative terms. Qualitative answers are converted to quantitative values according to sets of tables.

The model is intended to be population specific, so key inputs like total and/or region population size are required to be predefined, although user-defined values can also be input. A score is then calculated from the inputs, allowing the ranking of various food–pathogen combinations. The scoring system is designed to have a scale of 0 to 100, where 100 represents the worst imaginable scenario, i.e. that every member of the population consumes a lethal dose every day. A 0 score was arbitrarily set to equate to one mild diarrhoeal case per 100 billion people per hundred years, the logic being that the Earth's population is significantly less than 100 billion, so one would not expect to see an occurrence of the risk anywhere within a person's lifetime. The chosen range extends over 17.6 orders of magnitude, which equates to 100/17.6 ≈ 6 'risk ranking' units for each factor of 10 between risks.

The method has been designed to screen risks and to screen major categories of risk management options. The spreadsheet interface allows a risk manager to instantaneously consider what-if scenarios that can stimulate discussion of possible risk management strategies. The simplicity and generic nature of the model means that its results remain fairly crude. It also means that the questions that are posed are of a very general nature. The authors go into considerable detail to warn the reader of these limitations. There is, for example, no incorporation of uncertainty and variability in the model, though this could be added into the spreadsheet model using Monte Carlo simulation.

The tool was then used to evaluate 10 Australian seafood hazard+product combinations, and considered different consuming subpopulations in Australia, with the results shown in

[10] Available from http://www.foodsafetycentre.com.au/riskranger.php or through https://www.cbpremium.org/; accessed 6 December 2018

2787 Table 24 (from Sumner and Ross, 2002).

2788 The authors compared the ranked risks against observations in Australia. There had been no
2789 documented cases in Australia for risks with a score <32. All risks with scores between 32 and 48 (a
2790 range of three orders of magnitude) had caused several outbreaks of foodborne illness in Australia,
2791 with the exception of *Vibrio cholera*. Risks with scores >48 had all caused outbreaks of large
2792 numbers, some in specific regions.

2793

Table 24: Result of using RiskRanger to evaluate hazard+product combinations for various subpopulations in Australia (from Sumner and Ross, 2002).

Hazard+product pairing	Selected population	Risk ranking
Ciguatera in reef fish	General Australian population	45
Ciguatera in reef fish	Recreational fishers, Queensland	60
Scombrotoxicosis	General Australian population	40
Algal biotoxin in shellfish – controlled waters	General Australian population	31
Algal biotoxin — during an algal bloom	Recreational gatherers	72
Mercury in predaceous fish	General Australian population	24
Viruses in oysters — contaminated waters	General Australian population	67
Viruses in oysters — uncontaminated waters	General Australian population	31
Vibrio parahaemolyticus in cooked prawns	General Australian population	37
Vibrio cholerae in cooked prawns	General Australian population	37
Vibrio vulnificus in oysters	General Australian population	41
Listeria monocytogenes in cold-smoked seafoods	General Australian population	39
Listeria monocytogenes in cold-smoked seafoods	Susceptible (aged, pregnant, etc.)	45
Listeria monocytogenes in cold-smoked seafoods	Extremely susceptible (AIDS, cancer)	47
Clostridium botulinum in canned fish	General Australian population	25
Clostridium botulinum in vacuum packed smoked fish	General Australian population	28
Parasites in sushi or sashimi	General Australian population	31
Enteric bacteria in imported cooked shrimp	General Australian population	31
Enteric bacteria in imported cooked shrimp	Susceptible (aged, pregnant, etc.)	48

Key among the cautions the authors cite are that they have not been able to systematically and objectively evaluate the model's performance because there are few data sets describing exposure and foodborne disease incidence. That caution, however, is also evidence that full quantitative models would also not have been possible.

The authors also found that the model was a powerful tool for teaching the principles of risk analysis.

8.1.8 *Animal and animal product import-risk assessment methodology, Biosecurity Australia*

In 1998, a trade dispute between Canada and Australia over Australia's 24-year ban of uncooked salmon went to the WTO court (WTO, 1998). The Australia Quarantine Inspection Service (now Department of Agriculture and Water Resources) had produced a qualitative risk assessment analysing the disease threat in 1995, and another in 1996: the former assessed the risk to be acceptably low; the latter reached the opposite conclusion. The difference in conclusion came about through using a different qualitative risk assessment approach, rather than through the emergence of new information. The WTO Appellate Body came down on Canada's side because, *inter alia*, it considered that Australia had not implemented a proper risk assessment of salmon imports. This highlighted to the risk analysis community the potential problems of relying on a purely qualitative risk assessment methodology, especially in an adversarial environment.

Australia's regulatory body assessing import risk was re-structured, and it now falls under the responsibility of Biosecurity Australia. They have developed a semi-quantitative approach to assessing import risk (Biosecurity Australia, 2016). The risk evaluation is based on placing the estimated risk in a risk matrix. The band of cells marked 'very low risk' represents Australia's Appropriate Level of Protection (ALOP), or tolerance of loss.

The guidelines describe qualitative (e.g. low, medium, high), semi-quantitative (e.g. 0 → 0.0001; 0.0001 → 0.001; 0.001 → 0.01; 0.01 → 1) and quantitative (exact probability calculation) evaluation of likelihood of entry of an exotic disease into Australia. This has the potential advantage of using one environment to incorporate risk assessments along the qualitative to quantitative continuum. Qualitative evaluations of steps in a sequence that results in exotic disease entry are allowed through a matrix rule for combining such qualitative probabilities.

The consequence assessment component of the risk estimate for an exotic disease import risk is generally considered far more difficult than evaluating the probability of disease entry. This is because imports are regulated and fairly simple to model, and their probabilities are well understood, whereas there are no data on the spread of disease in the naïve country, and disease spread, is anyway, extremely complex to model.

Biosecurity Australia aimed to evaluate the probability and magnitude of a variety of impacts should the disease enter the country. They devised a series of rules that allowed the incorporation of the geographical extent of the consequence (local, district, regional, national), and the level to which the consequence would be felt at that scale. Other rules combined the (necessarily qualitative or semi-quantitative) estimates of likelihood of these consequences (given the disease has entered Australia) to allow a placement of the unrestricted risk estimate in the table (Table 25).

If the unrestricted risk (i.e. the risk from a product where no specific controls are in place to protect against the pathogen in question) estimate fell into an acceptable region, the import would be allowed without any restrictions. If not, restrictions (testing, heat treatment, evisceration, etc.) would be evaluated to determine the least trade-restrictive option that would allow the import product to meet Australia's ALOP.

Whichever approach (or combination of approaches) is chosen, the guidelines state that the approach should provide for the following:

- an assessment based on sound science;
- an assessment that is structured and transparent;
- an assessment that is internally consistent, and that can be repeated (with the same or a similar outcome) by another operator using the same framework and data;
- an outcome that will support the estimation of 'risk' (a combination of likelihood and consequences);
- an outcome that will enable risk to be evaluated against the importing country's ALOP, or 'tolerance for loss'; and
- a framework within which the efficacy of risk management and the acceptability of a mitigated risk can be evaluated.

Table 25: Tabulation of risk as a combination of likelihood and consequence (Biosecurity Australia, 2016).

Likelihood of pest entry, establishment and spread	Consequence of pest entry, establishment and spread					
	Negligible	Very Low	Low	Moderate	High	Extreme
High	Negligible risk	Very low risk	Low risk	Moderate risk	High risk	Extreme risk
Moderate	Negligible risk	Very low risk	Low risk	Moderate risk	High risk	Extreme risk

Low	Negligible risk	Negligible risk	Very low risk	Low risk	Moderate risk	High risk
Very Low	Negligible risk	Negligible risk	Negligible risk	Very low risk	Low risk	Moderate risk
Extremely Low	Negligible risk	Negligible risk	Negligible risk	Negligible risk	Very low risk	Low risk
Negligible	Negligible risk	Negligible risk	Negligible risk	Negligible risk	Negligible risk	Very low risk

8.1.9 *Multicriteria-based ranking for risk management of food-borne parasites, FAO/WHO*

FAO and WHO were asked to review the current status of knowledge on parasites in food and their public health and trade impact (FAO/WHO, 2014). This was done in order to provide the Codex Committee on Food Hygiene with advice and guidance on the parasite-commodity combinations of concern, issues that need to be addressed by risk managers, and the options available to them. As part of this charge some work was undertaken to develop a quantitative ranking tool using expert opinion.

The experts defined global criteria for evaluating the 24 food-borne parasites and rated each parasite along these criteria. The criteria were: (1) number of global illnesses; (2) global distribution; (3) acute morbidity; (4) chronic morbidity; (5) percentage chronic; (6) mortality; (7) increasing illness potential; (8) trade relevance; and (9) socio-economic impact. Each criterion was then weighted by the experts in importance. The three criteria for disease severity (3, 4 and 5) were combined into one criterion, giving a total of 7 criteria weights, reflecting the relative importance of each criterion to the overall score. The overall score for each parasite was calculated by normalized parasite criteria scores multiplied by fractional weights and summed. The resulting tool was able to give a global ranking of food-borne parasites by "importance" and their primary food vehicle.

Mean of elicited criteria weights used in the multi-criteria ranking are shown in Table 26 below. The overall score for each parasite is given by the following equation:

$$\text{Score} = C1*W1+C2*W2+\{C3*(1-C5)+C4*C5\}*W345+C6*W6+C7*W7+C8*W8+C9*W9$$

Table 26: Mean of elicited criteria weights used in the multi-criteria ranking (Table 3 from FAO/WHO, 2014).

Scoring Criterion		Criterion Weight
W1	Number of global food-borne illnesses	0.22
W2	Global distribution	0.14
W345	Morbidity severity	0.22
W6	Case-fatality ratio	0.15
W7	Increased illness potential	0.07
W8	Trade relevance	0.10
W9	Impacts on economically vulnerable communities	0.10

8.2 Examples of quantitative risk assessments

8.2.1 E. coli *O157:H7 in tenderized vs. non-tenderized beef, USDA-FSIS*

Mechanical tenderization, performed using stainless steel blades or needles, translocates pathogens from the surface of intact beef cuts to beneath the surface thereby potentially shielding those pathogens from the lethal effects of heat during cooking.

USDA FSIS aimed to estimate whether blade-tenderized steak posed a significantly greater risk than its equivalent non-tenderized steak (USDA-FSIS, 2002). They created a quantitative simulation model that predicted the change in survival of bacteria due to the extra protection that was afforded by being embedded in the meat through the tenderizing process. They estimated the bacterial load on steaks post-cooking and used this concentration as input into a dose-response model to estimate risk.

FSIS concluded that the probability of *E. coli* O157:H7 surviving typical cooking practices in either tenderized or not-tenderized steaks is minuscule and that differences in bacterial dose after cooking attributable to either type of steak were minimal. They predicted seven additional illnesses due to tenderization for every billion steak servings. This can be seen from Figure 9 below, where the dotted and solid lines for tenderized and non-tenderized steaks are virtually indistinguishable.

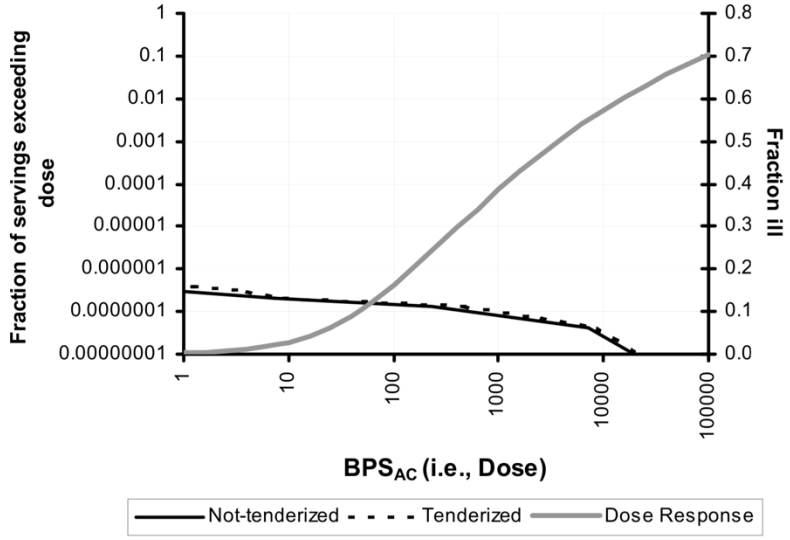


Figure 9: Model output showing predicted bacteria per serving after cooking (Dose) and corresponding frequency of illness (Dose Response).

This was a comparative risk assessment, so the model contained only the elements that were necessary to make the comparison. Thus, the model began with the distribution of bacteria on steak prior to tenderizing, and then looked at the difference in human health risk posed by the same steak under different processing. Consequently, there was no need to consider any factors involved in the rearing and slaughtering of the animal.

8.2.2 Listeria monocytogenes *in ready-to-eat foods, FAO/WHO*

FAO/WHO convened a drafting group to address three questions relating to *Listeria monocytogenes* that were posed by the Codex Committee on Food Hygiene (CAC, 2000).

Those questions were to (i) Estimate the risk of serious illness from *L. monocytogenes* in food when the number of organisms ranges from absence in 25 grams to 1,000 colony forming units (CFU) per gram or millilitre or does not exceed specified levels at the point of consumption; (ii) Estimate the risk of serious illness for consumers in different susceptible population groups (elderly, infants, pregnant women and immuno-compromised patients) relative to the general population; and (iii) Estimate the risk of serious illness from *L. monocytogenes* in foods that support its growth and foods that do not support its growth at specific storage and shelf life conditions.

The risk assessment (FAO/WHO, 2004) did not need to complete a full farm-to-fork model to answer these questions. The questions are also not specific to a particular country or product, which would require defining the scope of the model. The team decided to focus on the level of *Listeria monocytogenes* at retail; model the growth and inactivation from retail to consumption; and use a fitted dose-response function to estimate the subsequent risk.

The team selected four ready-to-eat foods to be reasonably representative of the many different foods available. The quantitative analysis produced the results shown in Table 27.

Table 27: Estimated risk from Listeria monocytogenes as used in the risk assessment (FAO/WHO, 2004).

Food	Cases of listeriosis per 10^9 people per year	Cases of listeriosis per 10^9 servings
Milk	910	0.5
Ice cream	1.2	0.0014
Smoked fish	46	2.1
Fermented meats	0.066	0.00025

The risk assessment report provides a very detailed explanation of the important limitations of the quantitative analysis, and, in particular, the need to rely on mostly European quantitative data on contamination, and on multiple sources for the prevalence estimates. Consumption data were mainly from North America, and the dose-response relationship was derived from epidemiological data from the United States of America. The summary response to the three Codex questions recognizes the caution that should be applied in interpreting the quantitative figures, by providing qualitative context.

> The report notes that the risk assessment demonstrates that most cases of listeriosis result from the consumption of high numbers of *Listeria*. Those cases arise from foods where the *L. monocytogenes* level exceeds the criteria (either 0.04 or 100 CFU/g). The model predicts that consumption of low numbers of *L. monocytogenes* has a low probability of illness. Eliminating higher levels of *L. monocytogenes* at the time of consumption has a large impact on the predicted number of illnesses. *(FAO/WHO, 2004):*

8.2.3 *Shiga-toxin-producing* E. coli *O157 in steak tartare patties, Netherlands*

Nauta *et al.* (2001) simulated the exposure the population in the Netherlands to Shiga-toxin-producing *E. coli* O157 in steak tartare, using a farm-to-fork Monte Carlo model. This risk assessment provided an example of integration of exposure assessment and hazard characterization with a low-level dose and an individual-level dose-response relation. The baseline model predicted 0.29% contaminated tartare patties and a mean dose of 190 CFU per contaminated patty, as shown in Table 28.

Table 28: Baseline risk model results at the stage of raw steak tartare patties, for different routes of exposure and the means for the Netherlands (NL). (Pos. tartare = STEC O157 contaminated steak tartare patty), where the column headers refer to specific segments of the Dutch industry (article 10 slaughter with 'industrial' butcher, article 10 slaughter with 'traditional' butcher and article 4 slaughter).

	Art 10, ind.	Art 10, trad.	Art 4	NL
Prevalence	0.29%	0.30%	0.21%	0.29%
Mean cfu/pos. tartare	3.4	670	1700	190

Pos. tartare with one cfu STEC O157	72%	38%	36%	64%

The dose-response model developed for the hazard characterization was based on a well-documented outbreak in a primary school in Japan (Shinagawa, Hu and Yoshida, 1997). An exponential model was fitted separately to the data for children and adults, resulting in point estimates for the probability of infection by a single cell of r = 0.0093 for children and r = 0.0051 for adults.

The exposure distribution was combined with the dose-response model in a Monte Carlo simulation by applying the single-hit model in the form $1-(1-r)^n$, with 'n' a random sample from the exposure distribution. The risk characterization predicted an attack rate of 0.0015% infections per person per year in the Netherlands; or 2,335 infections per 15.6 million people per year. This example incorporated variability but not uncertainty.

8.2.4 *Vibrio vulnificus in raw oysters, FAO/WHO*

An FAO/WHO assessment of the risk of illness due to *Vibrio vulnificus* in raw oysters adapted a risk model previously developed in the United States of America for *V. parahaemolyticus* (FAO/WHO, 2005). A principle objective was to investigate potential effectiveness of mitigations after development of a baseline model. This risk assessment provides an example of integration of exposure assessment and hazard characterization, with different assumptions used in estimating the dose-response.

A dose-response relationship for *V. vulnificus* was obtained by fitting a parametric model (Beta-Poisson) to estimated arithmetic mean risk for the population versus arithmetic mean dose (grouped by month and year). The magnitude of the difference between risk predictions obtained under these two alternative interpretations of the dose response is shown in Table 29. Assuming that the fitted population-level risk versus dose relationship applied at the individual level resulted in predictions of risk that were consistently lower (by up to 75%) than the epidemiological estimates of mean risks. The predictions of risk obtained based on an aggregate-level interpretation of the dose response were more consistent, on average, with the epidemiological estimates of mean risks used to obtain the dose-response fit, so this latter interpretation was used for risk characterization.

Table 29: Mean risk of illness due to Vibrio vulnificus per serving or exposure.

		Fitted as individual-level risk versus dose		**Fitted as mean risk versus mean dose**	
Season	**Estimated data based on case reports and consumption statistics**	**Risk**	**Ratio to Estimated Data**	**Risk**	**Ratio to Estimated Data**
Winter	1.40E-06	5.10E-07	0.36	1.10E-06	0.79
Spring	2.80E-05	1.70E-05	0.61	3.40E-05	1.21
Summer	4.90E-05	2.80E-05	0.57	3.90E-05	0.80
Autumn	1.90E-05	5.10E-06	0.27	2.30E-05	1.21

8.2.5 *Histamine in Fish Sauce, Thailand*

Fish sauce is a fundamental ingredient used in many Southeast Asian dishes and is also used as a dipping condiment. Due to the nature of raw materials and the production methods for traditional fish sauce, highs levels of histamine are found in many samples.

A risk assessment on histamine in Thai fish sauce was undertaken to respond to the request of the Codex Committee on Fish and Fishery products for sound scientific advice as a basis for the development of guidelines for the control of histamine in fish sauce (CCFFP, 2011).

Previous human trials and outbreak data were used to build a histamine dose-response model. The risk of developing histamine poisoning from fish sauce among Thai consumers was estimated. Consumption of fish sauce alone yielded a very small histamine intake to consumers. Different scenarios reflecting the effect of different histamine standards were also evaluated and are shown in the Table 30 below. As the analysis shows, the risk from fish sauce alone is essentially zero, and clearly less than the risk of histamine poisoning from fish alone. When the risk of histamine poisoning from fish plus fish sauce with two different standards was estimated, the risk increased slightly.

Table 30: Risk estimates using probabilistic approach (Table 5 in CCFFP, 2011).

Scenario	Mean risk per meal (SD)[a]
1. Fish sauce alone (a FS daily dose was consumed in 1 meal)	0.00 (0.00)
2. Fish alone[b] (a fish daily dose was consumed in a meal)	8.12×10^{-6} (0.4×10^{-5})
3. Fish + Fish sauce (a FS daily dose was consumed in 1 meal)	
• 200ppm FS standard	8.39×10^{-6} (0.46×10^{-5})
• 400ppm FS standard	8.47×10^{-6} (0.52×10^{-5})

[a] Risk per meal refers to the predicted risk of an individual becoming ill of histamine poisoning when he or she consumes a daily dose of fish sauce (FS) or a daily dose of a scombroid fish or a scombroid fish with fish sauce. The risk was estimated as a probability of the histamine intake to exceed the NOAEL limit of 50mg using Monte-Carlo simulations.

[b] Assumption: a fresh scombroid fish had a lognormal distribution with an average of histamine concentration of 5ppm and standard deviation of 10ppm.

8.2.6 *Pathogens in Fresh Vegetables, Rwanda*

This study analysed the "farm to fork" microbial risk for the fresh vegetable supply chain in Rwanda, (Ssemanda, 2018). One of the major data gaps identified by the authors was that they could not attribute the estimates of food related illnesses to any food vehicle based on the available data. Despite these limitations, the authors were able to evaluate several scenarios related to the distribution chain including: (i) moving all vegetables from farms to food service establishments without going through markets (ii) moving all vegetables from farms via supermarkets (with specialized refrigeration systems) to food service establishments (iii) holding all vegetables under refrigeration (2 and 8°C) from farm to fork and the introduction of a die off model (iv) all vegetables are effectively washed and sanitized, accomplished by increasing the modelled log reduction by washing (v) assuming no contamination and cross contamination occurs between vegetables and other surfaces throughout the chain (vi) assuming that preventive measures and interventions implemented at farm level reduce prevalence and levels of pathogenic *E. coli* by 90% and (vii) finally by assuming that the last three scenarios above are combined.

Simulation of the 7 "what if" scenarios described above resulted in varying fold-changes in the predicted microbial risk **Error! Not a valid bookmark self-reference.**. Improvement in washing and sanitization at food service establishments resulted in less than a 2-fold change in the predicted microbial risk. About a two-fold reduction in risk was observed for the what-if scenario of channelling all vegetables through supermarkets instead of traditional markets. Farm interventions reduced the predicted prevalence and levels of pathogenic *E. coli* in the base line model by 90%, introducing a cold chain and skipping the market step resulted in a tenfold reduction in predicted microbial risk. The what if scenario of avoiding contamination and cross contamination along the

supply chain led to a more than 4000-fold reduction in the predicted microbial risk. Lastly, combining the final three “farm to fork” measures resulted an estimated reduction in risk of 1 million.

Table 31: Number of illnesses per year and probability of illness per serving after 100,000 iterations of the baseline model and the what if scenarios (Table 6.4 in Ssemanda, 2018).

What if scenarios [b]	No. of illnesses per year (in millions)		Probability of illness per serving		Fold change[#]
	Mode	5th, 95th Percentile	Mode	5th, 95th Percentile	
Baseline/Route 1[a]	12.1	6.96, 32.6	0.100	0.0572, 0.169	–
Improving washing and sanitization at FSEs	10.63	2.13, 27.8	0.1039	0.0151, 0.156	1.14
Route 3	6.26	0.828, 17.3	0.0535	0.0395, 0.0057	1.93
Farm Interventions	1.13	0.517, 3.101	0.01029	0.00395, 0.0165	10.71
Introduction of cold chain	0.288	0.218, 15.1	0.00042	0.0015, 0.1016	42.01
Route 2 (market step skipped)	0.139	0.195, 10.87	0.000455	0.0013, 0.0728	87.1
No contamination and cross contamination along the supply chain	0.00272	0.00339, 9.4	0.0000183	0.0002, 0.0564	4,449
Farm to fork measures and interventions	0.00001108	0.0000144,0.694	7.33×10^{-8}	0.000, 0.00494	1.1×10^{6}

[a] Baseline model or Route 1 represents a simulation of the supply chain through which about 90% of the vegetables are channelled from farms via traditional markets to food service establishments (FSEs)

–, not applicable

#, Fold change were calculated by dividing the mode for the numbers of illness per year in the baseline model with the mode for the numbers of illness per year in the what if scenarios.

[b] What if scenarios arranged in descending order of the number of illnesses per year and probability of illness per serving.

8.2.7 *Campylobacter and Salmonella in Chicken Meals, Senegal*

The authors used a QMRA model to describe the risk of *Campylobacter* and *Salmonella* infection linked to chicken meals prepared in households in Dakar, Senegal (Pouillot *et al.*, 2012). The authors note that prevalence and concentration of pathogens in foods available in developing countries are well-known data gaps for risk assessment. They also suggest that more information on home cooking practices, cooking processes, and the length and temperature of food storage before and after preparation are needed. They used data collected specifically for purposes of QMRA, including prevalence and level of bacteria on chickens from local markets, time-temperature profiles of chickens from purchase to consumption, an observational data from meal preparation in kitchens, and data on pathogens prevalence on utensils, equipment and cooks' hands. Their model was developed in R software using the mc2d package for second-order Monte Carlo simulations. The simulation used 10,001 iterations in the variability dimension and 1,001 iterations in the uncertainty dimension. The model predicted that cross contamination led to a high expected frequency of pathogen ingestion, and that significant *Salmonella* growth was predicted during food storage at ambient temperature before and after meal preparation. The model also predicted a significant decrease in risk could be achieved through reducing prevalence of chicken contamination at slaughter, and by using simple hygienic measures in the kitchen. The model indicated that most effective modification to home cooking practices include the use of a new board, knife, and dish when manipulating the cooked chicken, assuming that these objects are bacteria-free. Figure 10 below illustrates the conceptual model used for quantitative exposure assessment for pathogens in households from the study.

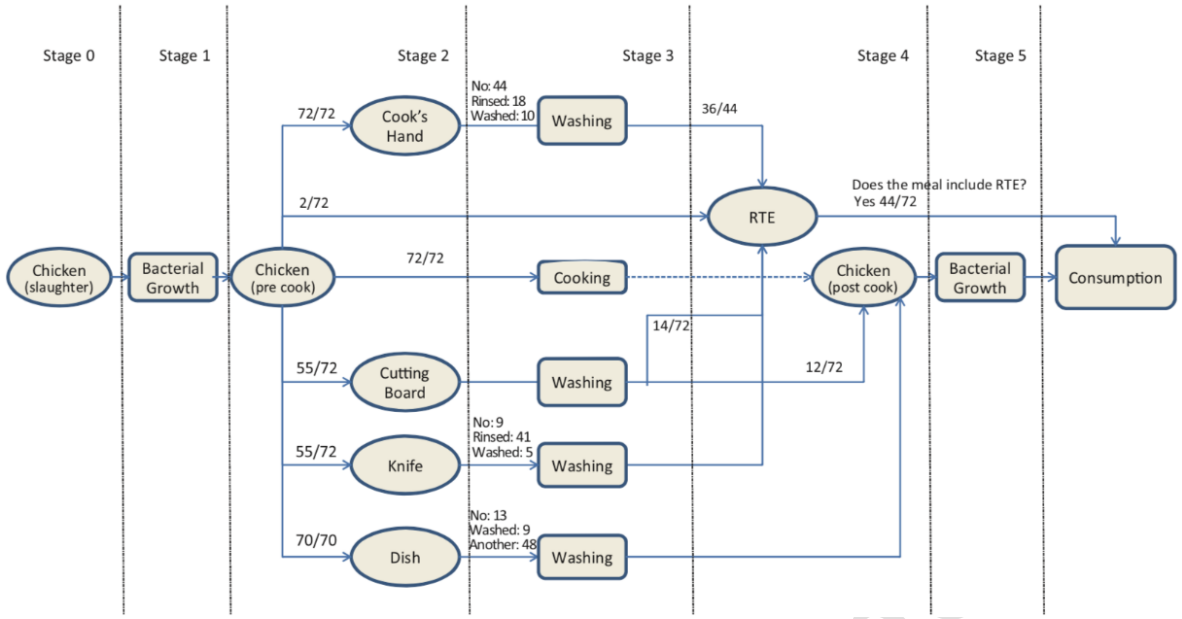


Figure 10: Model diagram of the quantitative exposure assessment for Campylobacter and Salmonella in Dakar households (Figure 1 in Pouillot et al., 2012)..

8.2.8 *Vibrio parahaemolyticus in bloody clams, Thailand*

A microbiological risk assessment of *Vibrio parahaemolyticus* risk from *Anadara granosa* (Bloody clam) was conducted by researchers from Thailand and Japan, who developed two risk assessments (a farm-to-fork model and a fractional change model) based on new data collected primarily from Hat Yai City in southern Thailand, where seafood consumption is popular. The QMRAs were published as part of the FAO/WHO Microbiological risk assessment series in a book entitled " Risk assessment of *Vibrio parahaemolyticus* in seafood (FAO/WHO, 2011a)".

The purpose of the risk assessment was to estimate the risk of *V. parahaemolyticus* infection associated with consumption of one type of seafood in a defined setting and during a limited period. The work documents an example of a case study in a developing country, where scientists were able to conduct a series of clinical and microbiological studies to generate locally relevant data and elaborate a risk assessment model for a non-oyster shellfish species.

The authors report that the study estimated that only a few people per 10,000 people per year acquire *V. parahaemolyticus* infection as a result of consuming the boiled Bloody clam food. The risk estimate does not support the common perception that Bloody clam is a major cause of diarrhoeal illness, including *V. parahaemolyticus* illnesses.

At the same time, the investigators caution that this study may also underestimate the risk of Bloody clam-associated *V. parahaemolyticus* illness due to several critical data gaps. The authors recommended that a case-control study be conducted using patients in Hat Yai City with microbiologically confirmed *V. parahaemolyticus* infections, as this could provide data on various food and environmental exposure paths. These investigations might also provide more realistic evidence of behaviour that reduces or increases the risk of *V. parahaemolyticus* illness. The investigators also suggested that more bacterial data on Bloody clam throughout the food chain should be collected, focusing on detection of virulent strains. Finally, the authors encouraged the collection of more detailed data on behaviour regarding harvesting, storage, cooking and consumption patterns need to be collected.

The figure below shows a representation of the model for a production-to-consumption QMRA for *V. parahaemolyticus* in Bloody clam.

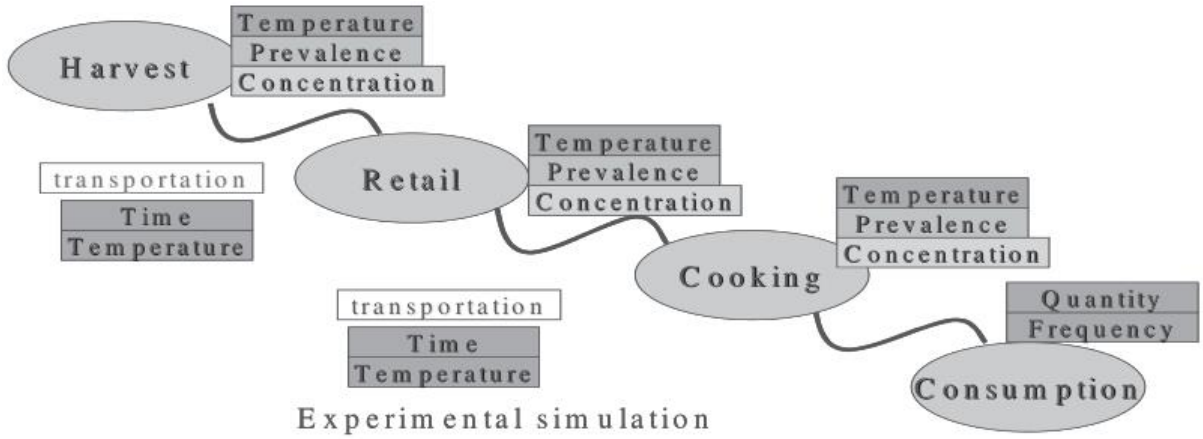


Figure 11: Schematic representation of the model framework for a production-to-consumption risk assessment of V. parahaemolyticus in Bloody clam (Figure II-6 in FAO/WHO, 2011a).

8.2.9 *Salmonella in table eggs, EFSA*

This risk assessment was developed by EFSA, the risk assessor, to answer a European Commission's (EC; the risk manager), question about the risk of *Salmonella* in eggs (EFSA, 2014b). The EC asked EFSA to assess the public health risk posed by *Salmonella* from table eggs and to quantify the relevance of the period of time between laying and consumption and the storage conditions of eggs. The period of time between laying and consumption is related with the "Sell-By date" and the "Best-Before date". The "Sell-By date" applicable to eggs is fixed at 21 days by the EU Hygiene Regulation. This means that table eggs must be delivered to the consumers within of 21 days after laying. The "Best-Before date" applicable to eggs is fixed in Regulation 589/2008 at 28 days from laying.

EFSA applied a quantitative risk assessment model for *S*. Enteritidis in eggs to answer the question. The quantitative model excluded all stages before laying. A baseline scenario was defined according to the current sell-by and best-before dates in the EU. Changes to time and temperature of storage at retail and in the household, were used to assess the impact storage practices as alternative scenarios (Table 32).

Table 32: Dates used in the model for the baseline and alternative scenarios (Table 11 in EFSA, 2014b)

Days post lay / Scenarios	Sell-by date (retail				Best-before date (household/catering)					
	21	28	35	42	28	35	42	56	63	70
Baseline	•				•					
Alternative 1		•			•	•	•	•	•	•
Alternative 2			•			•	•	•	•	•
Alternative 3				•			•	•	•	•
Alternative 4		◊			•	•	•	•	•	•
Alternative 5			◊			•	•	•	•	•
Alternative 6				◊			•	•	•	•
Worst-case scenario				•						•

• Scenarios with egg storage at retail under current conditions

◊ Scenarios with egg storage under refrigeration conditions in all retail establishments

Storage temperature and time were modelled using distributions based on expert opinion. The remaining distributions were adapted from the model using expert opinion distribution or based on scientific literature. Table 33 below shows a summary of time and temperature of storage of eggs in the EU, from farm to retail as derived from industry expert opinion.

Table 33: Summary of time and temperature of storage of eggs in the EU, from the 'on farm' to the 'transport to retail' stages as derived from expert opinion (industry experts) (Table 6 in EFSA, 2014b).

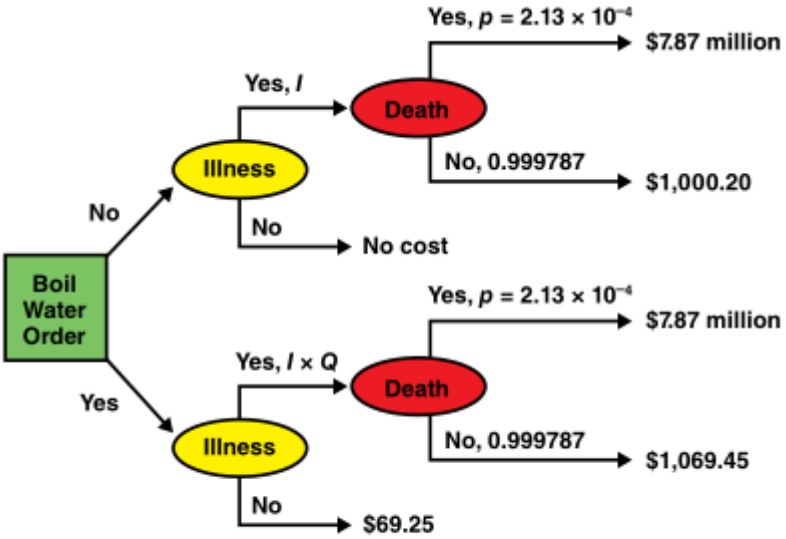
	Time (hours)			Temperature (°C)		
Stage	**Min.**	**Most likely**	**Max.**	**Min.**	**Most likely**	**Max.**
On farm	0	45	168	4	15	30
Transport to grading	0	6	48	4	15	30
Grading	0	18	168	5	15	30
Transport to wholesale	0	5	48	0.1	14	30
Wholesale/ distribution centre	0	23	336	0.1	13	28
Transport to retail	0	7.5	36	0	14	30

Extending the storage time for table eggs resulted in an increase in the number of illnesses, except when eggs are well-cooked. Extending the sell-by date by one week (from 21 to 28 days), but leaving best-before date unchanged, was estimated to result in a relative risk of illness of 1.4 and 1.5 for uncooked and lightly cooked egg meals respectively, compared to the baseline. If the best-before date was also extended by one week (from 28 to 35 days), the relative risk was 1.6 and 1.7. In the worst-case scenario considered in this assessment (sell-by date of 42 days, best before date of 70 days), the risks of illness were 2.9 and 3.5.

EFSA found that the implementation of refrigeration as currently used in the EU during the retail stage (i.e. with temperatures assumed to range from 0 to 12 °C) limited this increase in risk to some extent. The risk was reduced with an extension of up to three weeks in the sell-by date, and one or two weeks of the best-before date for a sell-by date of 35 and 28 days respectively if refrigeration was applied in all retail establishments. If the sell-by date or the best-before date were prolonged beyond three weeks, the risk estimates were greater, even if refrigeration at retail was applied, assuming that the proportion of consumers who do not store their eggs under refrigeration remained unchanged.

8.2.10 Cryptosporidium *in water – a cost-benefit analysis, United States*

The authors developed a simple decision tree (Figure 12) for *Boil Water Order* (BWO), including the effectiveness of the BWO as well as illness and death as possible outcomes (Ryan *et al.*, 2013). For each branch in the decision tree they assigned the relevant probabilities including the probability of illness, probability of death, and probability of the boiling process being ineffective, e.g. due to too short a boiling time or boiled water being transferred to a nondisinfected container, or other factors. Estimates for these probabilities, and for costs of implementation and for the various outcomes were based on published literature, including from the United States Environmental Protection Agency, and the uncertainty in these estimates were evaluated using a Monte-Carlo sensitivity analysis.



***I*—the probability of illness, *Q*—the probability that the boil water order is ineffective, *p*—the probability of death from illness, 0.999787—the probability of no death from illness**

Figure 12: Decision tree for Boil Water Orders for Cryptosporidium *showing the probabilities and estimated costs for illness and death outcomes (Ryan* et al.*, 2013).*

The authors used the decision tree to calculate a threshold value for the oocyst concentration in treated water using an exponential dose response model; this was done by equating the BWO and No BWO branches and solving for the daily dose and associated concentration. The authors concluded that this threshold concentration was equal to 0.046 oocysts/L in treated water or 46 oocysts/L in raw water, which was considered to be more practical to assess using water sampling. These concentrations were estimated to result in 9 illnesses per 10,000 people exposed, given the assumed 3-$\log_{10}$ reduction during water treatment. However, the authors also noted that "many water supplies that exceed this concentration may already be applying additional treatment, given that a concentration of 46 oocysts/L would require treatment beyond the 3-log removal required by the Long Term Enhanced Surface Water Treatment Rule."

Part 2 Detailed Considerations

9. Qualitative: semi-quantitative: quantitative

9.1 Qualitative risk assessment

There are several examples of published qualitative risk assessments (e.g. Lake *et al.*, 2009; King, Lake and Cressey, 2011), although they tend to elicit less scientific attention than quantitative risk assessments.

It should be emphasized that the attributes of good risk assessment, as described in Chapter 3, apply equally to qualitative risk assessment. Appropriate data must be collected, documented and fully referenced and synthesized in a logical and transparent manner whichever method is employed.

Despite a number of large and well-publicized quantitative microbiological food safety risk assessment projects that have been completed, it is probable that the majority of risk assessments utilized by risk managers and policymakers in the fields of food safety, health and microbiology are not fully quantitative in the sense described in Chapter 3.

There may be a variety of reasons for this. Quantitative microbiological risk assessment is a specialized field and methods are still being developed, and the expertise and resources to complete them are not widely available. Equally, as noted earlier, the results of such assessments are not always 'accessible' to risk managers and other stakeholders. Thus, where a formal risk assessment (i.e. a body of work presented in a way that conforms to a set of risk assessment guidelines and specifically designed to estimate the magnitude of a risk) is commissioned by a risk manager, a qualitative risk assessment may be specified for reasons including:

- a perception that a qualitative risk assessment is much quicker and much simpler to complete;
- a perception that a qualitative risk assessment will be more accessible and easier for the risk manager or policymaker to understand and to explain to third parties;
- an actual or perceived lack of data, to the extent that the risk manager believes that a quantitative assessment will be impossible; or
- a lack of mathematical or computational skills and facilities for risk assessment, coupled with a lack of resources or desire to involve an alternative or additional source of expertise.

Whatever the reasons, many of them involve perceptions about the process of defensible qualitative risk assessment that, for reasons also mentioned above, are frequently not valid. Data and knowledge are required for any type of risk assessment, irrespective of whether qualitative, semi-quantitative or quantitative approaches are used. Numerical data are preferred, and a lack of appropriate crucial data will affect all approaches adversely. As data collection and documentation is usually the most time-consuming part of any risk assessment, and defensible logic is required to synthesize the data into an estimate or conclusion concerning the risk, a qualitative risk assessment will not necessarily be quicker or simpler to complete. In many cases, however, qualitative and semi-quantitative risk assessments are quicker to complete, and, whilst they require an equal degree of logic and considerable numeracy, they require fewer specialized mathematical and computational resources. A qualitative risk assessment has descriptions of the probability of an unwanted outcome in terms that are by their very nature subjective. It means that it is not necessarily easier either for the risk manager to understand the conclusions obtained from the risk assessment, or to explain them to a third party. Crucial to any formal risk assessment method is transparency, whether to describe how a numerical or a qualitative description of risk was achieved, because this enables

users to understand the basis of the assessment, to understand its strengths and limitations, to question or critique the assessment, or provide additional data or knowledge to improve the assessment. Additionally, because all approaches also require specialized medical, microbiological, biological, veterinary, epidemiological and other expertise, the inclusion of information and concepts from such a wide variety of areas of knowledge can make the risk assessment less accessible. Section 16.5 contains information about ways in which the results of risk assessment can be communicated.

9.1.1 *The value and uses of qualitative risk assessment*

Risk assessment, at its simplest, is any method that evaluates, or attempts to evaluate, a risk. Qualitative risk assessment is not, however, simply a literature review or description of all of the available information about a risk issue: it must also arrive at some conclusion about the probabilities of outcomes for a baseline risk and/or any reduction strategies that have been proposed. Both CAC (1999) and OIE (2018) state that qualitative and quantitative risk assessments have equal validity, though they did not specifically consider semi-quantitative risk assessment. However, neither organization explains the conditions under which qualitative and quantitative risk assessments are equally valid, and there is debate among risk experts about methods and approaches to be applied for qualitative risk assessment, and criteria for their validity. The World Trade Organization Committee on Sanitary and Phytosanitary Measures notes some advantages of quantitative expressions of risk (WTO, 2000):

> *"... quantitative terms, where feasible, to describe the appropriate level of protection can facilitate the identification of arbitrary or unjustified distinctions in levels deemed appropriate in different situations ... use of quantitative terms and/or common units can facilitate comparisons."*

However, when developing risk assessments, numerical results should be explained and put in context with a discussion of the limitations of the data and analysis, the important assumptions made, and the qualitative aspects of the risk not illuminated by quantitative analysis. The same underlying logic applies whether the assessment is quantitative or qualitative.

It is sometimes the case that a qualitative risk assessment is undertaken initially, with the intention of following up with a quantitative risk assessment if it is subsequently thought to be necessary or useful.

It may be the case that a qualitative assessment provides the risk manager or policymaker with all the information they require. For example, perhaps the information gathered includes some piece of evidence that shows that the risk is effectively indistinguishable from zero, and no more need currently be done. Or, conversely, perhaps evidence shows that it is obviously unacceptably large, or that one or more consequences are so unacceptable that safeguards are needed whatever the magnitude. Analogously, qualitative assessments can be used as a first step to quickly explore or implement protective measures where there is expert consensus that such measures would be immediately effective and useful. As such, if there are obvious sources of risk that can be eliminated, one does not need to wait for the results of a full quantitative risk assessment to implement risk management actions. A qualitative risk assessment may also provide the necessary insights into the pathway(s) associated with the risk of concern, but not previously identified, which also allows the risk manager to make decisions or apply safeguards without further quantification.

FAO/WHO (2004) noted:

> *"Qualitative risk assessments may be undertaken, for example, using the process of 'expert elicitation'. Synthesizing the knowledge of experts and describing some*

uncertainties permits at least a ranking of relative risks, or separation into risk categories. … As assessors understand how qualitative risk assessments are done, they may become effective tools for risk managers."

Noting that, in some circumstances, such as those indicated above, they can be conducted quickly and used to address specific questions and may reveal that an extensive, fully quantitative exposure, and risk assessment is not required to provide relevant advice to the risk manager.

9.1.2 *Qualitative risk assessment in food safety*

Qualitative risk assessments have been extensively used in import risk assessments of animals and of animal products (OIE, 2018). Many animal products are also food intended for human consumption; therefore, many of these import-risk assessments have also involved food products intended for human consumption. However, the focus of such import-risk assessments has historically been to assess the risk of a particular exotic pathogen entering a potential importing country or region, carried within the food in question. The intention is generally to assess whether the risk of importing the pathogen in the product is too high to be acceptable to the importing country, and whether safeguards should therefore be applied (such as cooking, freezing, testing or total ban). Frequently, further consequences, in particular any potential consequences to human health, have not been the focus of the risk assessment, even when the pathogen might be a zoonotic organism.

Food product import-risk assessments, in general, assess the probable presence of a pathogen in that product, so that if this probability is unacceptable, then import safeguards can be applied. Human health and safety risk assessments of food products, in general, not only set out to assess the probability of the presence of a pathogen, but also the amount of pathogen present, so that the human response to the probable dose can be assessed. The latter aspect is sometimes perceived to make qualitative risk assessments less useful in food safety applications, despite the fact that many quantitative dose-response data are very subjective in their estimation methods. However, not all steps in the risk assessment process (i.e. Hazard Identification, Hazard Characterization, Exposure Assessment, Risk Characterization) are necessary in all cases to assist food safety risk managers to deduce appropriate risk management actions. Actions to reduce exposure, even in the absence of dose-response data, would in many cases be appropriate risk management steps and could be determined from an 'incomplete' risk assessment (i.e. no Hazard Characterization), whether qualitative or quantitative. An epidemiologically based risk assessment may also not require dose-response data.

9.1.3 *Characteristics of a qualitative risk assessment*

The complementary nature of qualitative and quantitative risk assessments

The main principles of a risk assessment apply equally anywhere along the qualitative to quantitative risk assessment continuum. These include identification of the hazard, defining the risk question, outlining the steps of the risk pathway, gathering data and information, including information on uncertainty and variability, combining the information in a logical manner, and ensuring all is fully referenced and transparent. It follows from this that many of the activities are the same, up to and including the gathering of the data. Therefore, it is sometimes the case that a qualitative (or semi-quantitative) risk assessment is included in a risk profile, with the intention of following up with a quantitative risk assessment if it is subsequently thought to be necessary, or useful, and feasible.

The detailed investigative nature of a qualitative risk assessment may provide the risk manager or policymaker with all the information they require. A qualitative risk assessment may also provide the necessary insights into previously unidentified pathway(s) associated with the risk of concern, which allows the risk manager to make decisions or apply safeguards without further quantification. In

these circumstances additional quantitative assessments will probably be deemed unnecessary by the risk manager or policymaker.

A qualitative risk assessment can be informative even if a quantitative assessment is being planned. It can be used to identify the data currently available, the uncertainties surrounding that data, and uncertainties about exposure pathways, to decide if quantification is both feasible and likely to add anything to the current state of knowledge. It can identify areas of data deficiency for targeting future studies necessary prior to quantification. It can examine the probable magnitude of the risks associated with multiple risk pathways, such as exposure pathways, prioritizing them for the application of quantification.

Whatever the initial intention, when a qualitative risk assessment has already been undertaken, much of the work for a quantitative risk assessment has already been done. For the same risk question, quantification will be able to build on the risk pathway(s) and data already collected, to provide a numerical assessment of the risk.

Subjective nature of textual conclusions in qualitative risk assessments

Assessing the probability of any step in the risk pathway, or the overall risk, in terms of high, medium, low, negligible, etc., is subjective, as the risk assessor(s) will apply their own concepts of the meanings of these terms. These meanings may (and probably will) differ from person to person. This is one of the major criticisms levelled at qualitative risk assessments. However, these final risk assessors' estimates should never be viewed in isolation, just as numerical outputs from quantitative risk assessments should not, and reinforces the need for transparent documentation of the data and logic that lead to the assessor's estimate of the risk.

For a qualitative description of a risk to be useful to a risk manager, the assessor and manager must have similar perceptions of the meaning of subjective terms such as 'low', negligible', etc., or other descriptors (see also Section 7.2). A final risk characterization label, e.g. 'low', is largely meaningless to a risk manager without some sort of indication of what constitutes 'low' in the eyes of the author of the report. Also, it gives little indication of what particular pieces of evidence would change the assigned label to something other than 'low'. Thus, if evidence were to be presented that 25% of the product was not stored frozen, would the risk increase to moderate? Judgements will be used within any risk assessment. These may be the risk assessor's judgements, or expert opinion, or both, and these will always be subjective. This will apply when defining the scope of the problem, selecting (and rejecting) data, delineating the risk pathways, applying weightings to data or model pathways, selecting the distributions in a stochastic model, etc., as well as selecting a description of high, low, etc., in a qualitative assessment. Therefore, any risk manager, policymaker or other stakeholder who needs to use, or wishes to understand, a given risk assessment, irrespective of where on the qualitative to quantitative spectrum the risk assessment lies, should not simply look at the final 'result'. They should have some knowledge of how that result was arrived at.

Many people may not have the knowledge base to directly understand the computations involved within a quantitative risk assessment. They will need to rely on the explanations and opinions of the risk assessor in explaining to them how the result was reached, and what the underlying assumptions, judgements, uncertainties, etc., in the computation were. If the risk assessor is a good teacher as well as a good risk assessor, this can work well. But only under these circumstances are the risk managers likely to be able to decide for themselves the significance and meaning of the quantitative result.

As noted previously, the mathematical expression of risk inherent in a quantitative risk assessment may limit accessibility, unless accompanied by narrative explanations. Analogously, with a qualitative assessment, providing it has been written in a transparent and logical way, almost anyone should be able to understand and follow the arguments.

A definition of 'negligible' used in qualitative risk assessment is that, for all practical purposes, the magnitude of a negligible risk cannot, qualitatively, be differentiated from zero (for example, see the use of the term in OIE (2018). The term 'zero' is not used because in microbiological food safety there is generally no such thing as absolutely no risk. Note that, since 'negligible' may be understood as 'may be neglected', it can be argued to be a 'risk management' term because it involves a judgement.

It must be emphasised, that qualitative risk assessment relies on as much numerical data as possible to provide model inputs despite their textual nature, and the process of data gathering must be equally as thorough as for a quantitative risk assessment.

9.2 Semi-quantitative risk assessment

Semi-quantitative methods involve assigning labels to qualitative estimates in the form of probability ranges, weights or scores, and combining them by addition, multiplication, or other mathematical operation with the objective of achieving a greater level of objectivity compared to qualitative approaches. There must be a clear set of rules that dictate how the labels (scores, weights, ranges etc.) are combined. This set of rules should follow the basic probability principles, and be fully described and transparent regarding operation, and result generation. This provides an intermediary level between the textual evaluation of qualitative risk assessment and the numerical evaluation of quantitative risk assessment. It offers a more consistent and rigorous approach to assessing and comparing risks and risk management strategies than does qualitative risk assessment and avoids some of the greater ambiguities that a qualitative risk assessment may produce and it does not require the same mathematical skills as quantitative risk assessment. Semi-quantitative may be an attractive option when data are limited, but it should be noted that all forms of risk assessment require the greatest possible collection and evaluation of data available on the risk issue, and food safety risk assessments require in-depth knowledge in a variety of scientific disciplines. Semi-quantitative risk assessment requires all of the data collection and analysis activities for qualitative risk assessment as described in the previous section. It has been stated that semi-quantitative methods do not offer any advantages over well-researched, transparent, peer-reviewed qualitative approaches (OIE, 2018).

As noted in the previous section, Codex Alimentarius Commission (CAC) and others generally consider just two categories of risk assessment: qualitative and quantitative. Semi-quantitative risk assessment, as described here, has often been grouped together with qualitative risk assessment, but this understates the important differences between them in their structure and their relative levels of objectivity, transparency and repeatability.

9.2.1 *Uses of semi-quantitative risk assessment*

Semi-quantitative risk assessment is most useful in providing a structured way to rank risks according to their probability, severity or both (risk), and for ranking risk reduction actions for their effectiveness. This is achieved through a predefined scoring system that allows one to map a perceived risk into a category, where there is a logical and explicit hierarchy between categories.

Comparing hazards

One example of the utility of the semi-quantitative risk matrix approach is a probability-severity table. This approach offers quick way to visualize the relative riskiness (a term sometimes used for the combination of probability and severity) of several identified hazards within the domain of analysis. Table 34 illustrates an example, where all hazards (e.g. the list of pathogens that might appear in a particular food type) are recorded in one table, allowing for the easy identification of the most threatening hazards (those closer to the upper right corner) as well as providing a general picture of the overall risk associated with the food type. The numbers in the table are indices for identified hazards. Hazards 2 and 13, for example, have high risk; hazards 3 and 7 have very low risk. Hazards with zero events per year (i.e. zero probability; hazards 11 and 14) or no severity (hazards 8, 9 and 10) do not pose a risk, but may be useful to document as having been identified and subsequently determined to have negligible risk.

Table 34: Example of a P-I table for individual hazards (indicated by the numbers in the grid) per year (NIL=None, VLO = Very Low; Lo = Low; Med = Medium; Hi = High; VHI = Very High).

Severity							
	VHI			6			13,2
	HI	14				15	12
	MED		5		4	1	
	LO						
	VLO	11	7	3			
	NIL			8,9		10	
		NIL	**VLO**	**LO**	**MED**	**HI**	**VHI**
		Events per year					

Risk scores can then be used to rank the identified risks. A scaling factor, or score, is assigned to each label used to describe each type of severity. If a log scale is used to define each categorical scale, as in the example provided in Table 11 for probability, the probability and severity scores can be designed such that the risk score equals their sum, or some other simple mathematical equation. Table 35 provides an example of the type of scaling factors that could be associated with each probability and severity combination.

Table 35: Example risk score calculations for some hazards used in from Table 34.

Risk Index	Probability	Probability Score	Severity	Severity Score	Risk Score
13	VHI	5	VHI	6	5+6=11
1	HI	4	MED	3	4+3=7
5	VLO	1	MED	3	1+3=4

Comparing risks and risk management strategies

Semi-quantitative risk assessment is generally used where one is attempting to optimize the allocation of available resources to minimize the impact of a group of risks under the control of one organization. It helps achieve this in two ways: first the risks can be placed onto a sort of map so that the most important risks can be separated from the less important; second, by comparing the total score for all risks before and after any proposed risk reduction strategy (or combination of strategies) one can get a feel for how relatively effective the strategies are and whether they merit their costs.

Table 14 shows how a risk matrix might be separated into three regions. This is sometimes known as a 'traffic light' system: hazards lying in the green area are well within an acceptable level (low risk);

hazards lying in the red region are not acceptable (high risk); and the remaining hazards lie in the amber, or the medium risk, area. The crudeness of the scaling of this semi-quantitative risk assessment approach means that it will often be appropriate to study 'amber risks' further, perhaps using more quantitative methods, to determine whether they actually lie close to or within the red or green regions.

9.2.2 *Characteristics of a semi-quantitative risk assessment*

Categorical labelling is the basis for semi-quantitative risk assessment. It uses non-technical descriptions of a risk's probability, severity, and risk (the combination of probability and severity), for example: 'Very low', 'Low', Medium', 'High', and 'Very High', or some scaling like A-F. For this type of labelling to be unambiguous and useful, risk managers must provide a list of the non-overlapping, exhaustive categorical terms that are to be used, together with clear definitions of each term. For example, a 'Low' probability might be defined as an individual having between 10^{-3} and 10^{-4} probability of occurring in a year, and a 'High' severity might be defined as an individual suffering long-term sequelae that materially affect their quality of life. This step is crucial, as a number of studies have shown that even professionals, who are well-versed in probability ideas and who regularly make decision based on risk assessments, have no consistent interpretations of probability phrases ('likely', 'almost certain', etc.). This lack of consistent interpretation could lead to inconsistent assessment of risk and inadvertent lack of transparency. Without numerical definitions of probability, subjective descriptions such as 'low' can be affected by the severity: for example, a 5% probability of diarrhoeal illness from some exposure might be considered 'low', but a 5% probability of death from an exposure might be considered 'high'. The number of categories used to express probability and severity should be chosen so that one can be sufficiently specific without wasting time arguing about details that will not ultimately affect the risk management decision. A five-point scale has been the most commonly used in the risk community, sometimes with a sixth category representing zero for probability and severity, and a seventh 'certain' category for probability representing a probability of 1.

Often, in the course of carrying out a qualitative risk assessment, one can roughly estimate the probability of exposure, etc., from comparison with other, previously quantified risks or from good data pertaining to the problem in hand. If time or the available data are insufficient to carry out a complete quantitative risk assessment, one can use these categorical labels to express the risk level in a more structured way than a simple, qualitative description of the evidence one has acquired. An example is presented in Section 7.3.2.

9.2.3 *Limitations of semi-quantitative risk assessment*

A semi-quantitative risk assessment has its limitations and can cause errors in conclusions (see Cox Jr., 2008; Levine, 2012; Vatanpour, Hrudey and Dinu, 2015 for discussion on the issues with an emphasis on risk matrices). Issues arise from several difficulties in defining how categorical labels should be interpreted and manipulated. The risks are placed into usually quite broad sets of categories: it is common to use five or so for probability and for severity, not including zero, which gives 25 possible combinations. It is therefore imperative that the categories are carefully constructed. For example, one could break up the probability range into five categories, as in Table 36.

Table 36: A linear scoring system for probability.

Score	Probability range
1	0 – 0.2
2	0.2 – 0.4

3	0.4 – 0.6
4	0.6 – 0.8
5	0.8 – 1

However, under this scheme, a risk with a probability of 0.1 would sit in the same category (Score 1) as a risk with probability 0.000001, despite being 100 000 times more likely. This is one reason why a log scale is often chosen for probabilities. The nature of food safety risk means that often deals with probabilities that span several orders of magnitude, which also makes the use of a log scale more appealing and informative.

It cannot be easily combined probability scores for components of a risk pathway to get a probability score for the risks as a whole. For example, food safety risk estimation is often split into two parts: the probability of exposure; and the probability of illness given exposure. Using the scheme above, if the exposure had a 0.3 probability (score = 2) of occurring within a certain period for a random individual, and the probability of illness from that exposure was 0.7 (score = 4), the combined probability is 0.21 (0.3×0.7=0.21, which receives a score 2). It cannot be easily created a rule with scores that replicates the probability rules, and this limitation is well recognised (see references above). Taking the minimum of the two scores is one partial solution, but this generally over-estimates the risk. For example, changing the probability of illness given exposure to anything from 0.2 to 1.0 would give the same combined probability score of 2 using this approach.

The use of a log scale for probability relieves the problem to some extent if it is reversed the probability score order described so far to assign the highest probability with the lowest score, as shown in Table 37.

Table 37: A logarithmic scoring score order described so far to assign the highest system for probability.

Category	Probability range	Score
Negligible	Indistinguishable from 0	NA
Very Low	$< 10^{-4}$, (except 0)	5
Low	10^{-4} to 10^{-3}	4
Medium	10^{-3} to 10^{-2}	3
High	10^{-2} to 10^{-1}	2
Very High	$> 10^{-1}$ (except 1)	1
Certain	1	0

Using this scheme, the scoring system equivalent of multiplying probabilities is to add scores. For example, if the exposure had a 0.2 probability (score = 1) of occurring within a certain period for a random individual, and the probability of illness from that exposure was 0.004 (score = 3), the combined probability is 0.0008 (score 4). It does not always work out so neatly, however. An exposure with probability 0.5 (score = 1) and a probability of illness from that exposure of 0.003 (score = 3) gives a combined probability of 0.0015 (score = 3), yet the individual scores sum to 4. Adding scores in a log system like the one in Table 37 will often over-estimate the probability by one category. This is one reason for having an amber region in the traffic light system, because risks may be over-estimated, and risks falling into an amber region may in fact turn out to be acceptable.

There is also a problem of the granularity of the scale. For example, for a risk whose probability of occurrence falls just above the boundary between two categories, and for which a risk management strategy reduces that probability by a small amount, it could be dropped down one probability

category, which is now indistinguishable from reducing the probability by a factor of 10. However, there is nothing to stop the risk assessor from using score fractions if it seems appropriate. The integer system is designed for convenience and simplicity and could be changed to include fractions if this better represents the available knowledge.

Using the semi-quantitative risk assessment scoring system as a surrogate for probability calculations is also likely to cause more severe inaccuracies when one assesses a longer sequence of events. This is because the "errors" are being compounded; see for example the "Probabilities Are Inconsistent with Qualitative Aggregation Rules" (Cox Jr., Babayev and Huber, 2005)

10. Data

Risk assessment studies are developed by compiling information from a variety of data sources. Each of these data sources contributes in varying degrees to an understanding of the pathogen-host-matrix interactions (Figure 4) that influence the potential public health risks attributable to a disease agent. An appreciation of the strengths and limitations of the various data sources is critical to selecting appropriate data for use, and to establishing the uncertainty associated with different data sets and test protocols.

Active data collection is often required, because reliance on passive data submission or data in published form does not usually provide enough information in sufficient detail to construct the QRA model. Relevant data come preferably from peer-reviewed journals. In case of lack of data or insufficient data from published sources, it is also advisable to evaluate the availability of unpublished, high-quality data sources. Risk assessors should communicate with experimenters, epidemiologists, food or water safety regulators, and others who may have useful data that could contribute to the analysis. An example is the outbreak information collected by the Japanese Ministry of Health (Kasuga *et al.*, 2004) and which was used for dose-response modelling of *Salmonella*, along with other data (FAO/WHO, 2002a). When such data are used, the criteria and results of evaluation must be carefully documented. If using material published on the Internet, care should be taken to establish the provenance, validity and reliability of the data, and the original source, if known.

Understanding the characteristics of data sources is important to the selection and interpretation of data. Risk assessors often use data for a purpose other than that for which it was originally intended. Risk assessors and modelers need to know how the data they use were collected, and the purpose of their collection. The properties of the available data will depend on the perspective of the researchers generating the data (e.g. experimenter versus epidemiologist).

Two categories of data are necessary for the development of a risk assessment model: firstly, data that, in text format, describe the biological and physical processes as well as the human factors involved, and, secondly, numerical data that allow quantitative estimates to be calculated. The extent to which numerical data are required will vary from one risk assessment to another, depending on the defined purpose, scope, modelling approach and details chosen. In Table 38 an overview is presented of the types of data required for conducting a risk assessment as well as their collection sources and these are described in detail in the following sections.

3511 *Table 38: Data required for risk assessment and data collection sources*

Type of Data	Description	Collection Source
Hazard Identification		
Association between exposure and adverse health outcome	The evidence that can be utilized to pair the food and microbiological hazard and link the exposure to hazard in specific food to human illnesses	• Outbreak data • Foodborne disease surveillance and annual health statistics • Food safety rapid alert systems • Literature: Analytical epidemiological studies • Systematic food contamination monitoring surveys
Microbiological hazard characteristics	Characteristics of the organisms and mechanism with which the organism affects the host are described, while detailed dose-response analysis is done in hazard characterization	• Literature: microbiological studies
General characteristics of food and conditions of supply chain	Intrinsic characteristics of the food (e.g. pH, water activity) and process evaluation (e.g. time, temperature)	• Industry data and literature: Description of product and food supply
Adverse health outcomes in exposure population	Disease and sequelae in population and sub-populations by demographic and/or social-economic factors, sensitive population	• Scientific and medical literature
Hazard Characterization		
Parameters of dose response models	Parameters estimated by fitting to dose-response data to models	• Literature: dose-response fitted models
Dose response data	Data on dose response that can be fitted to a dose-response model	• Outbreak data • Volunteer feeding studies • Animal studies
Annual cases of the foodborne illness and prevalence of the pathogen in a food commodity	Data on reported cases of illness and prevalence of the causing pathogen in the food commodity to approximate a DR relationship	• Foodborne disease surveillance and annual health statistics • Systematic monitoring surveys
Exposure Assessment		
Prevalence and concentration	Data on prevalence and concentration of the pathogen in the food of concern at the starting point of the risk assessment and other points of the food chain	• Systematic food contamination monitoring surveys • Literature: prevalence and concentration surveys • Expert Knowledge Elicitation (EKE)

Type of Data	Description	Collection Source
Processing conditions	Data describing the conditions of food processing which may affect prevalence and concentration of the pathogen (i.e. time-temperature of thermal processing, fermentation, partitioning, etc)	• Literature: Description of product and supply chain • Industry data: Description of product and supply chain • EKE
Effect of processing stages and/or interventions	Data on the effect of a processing stage/intervention on prevalence and concentration of the pathogen	• Literature: Intervention studies • EKE
Product characteristics	Data on food characteristics (pH, aw, concentration of antimicrobials, packaging atmosphere, use-by-date, etc.) that may affect the behaviour of the pathogen during storage	• Literature: Description of product and supply chain • Industry data: Description of product and supply chain • EKE
Distribution and storage conditions	Time-temperature data for distribution and storage of the food at retail and domestic level	• Literature • Industry data: Description of product and supply chain • EKE
Conditions of food handling and preparation	Data describing the conditions of food handling and preparation which may affect prevalence and concentration of the pathogen (i.e. time-temperature of cooking, partitioning, etc.)	• Literature: cross contamination, food handling and preparation • EKE
Kinetics of pathogen's behaviour	Data on the kinetics of pathogen's growth/survival/inactivation during food processing, distribution, storage, handling and cooking.	• Literature: predictive microbiology models • Modelling online tools
Consumption	Data on serving size Data on frequency of consumption, and number of annual servings for different population groups (normal, susceptible, pregnant, etc.).	• National consumption databases • EKE • Total diet studies
Population segments	Data on population size by segments	• National population census
Annual production of the food commodity	Data on tons of food produced in a country and information of imports, if necessary	• National food production statistics
Risk Characterization		
Annual cases of the foodborne illness	Data used for anchoring and/or validating a risk assessment model	• Foodborne disease surveillance and annual health statistics

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Data should be collected to represent reality as closely as possible. The same principles can be applied, for instance, to fisheries as to primary production, or to food service (catering) as the point of consumption, as well as for issues related to waterborne microbiological hazards. Note that the specific scope and purpose of a risk assessment can be much narrower in practice and these will determine the type and detail of data required. Since data are not available in all instances, alternative (surrogate) data may be employed. It is important to clearly describe the rationale and suitability for selecting the alternative data and evaluate the influence of using such data on the final risk estimates (Chapters 14 and 15)..

This chapter presents a summary of the types of data typically required for the construction of a risk assessment, capturing in brief the strengths and limitations of each of several classes of data sources.

10.1 Literature (primary and/or meta-analysis)

Data required for risk assessments may come from a wide variety of published sources, some of which may be common to many countries. Academia and other organizations publish their findings in the public domain. This can be in the form of documents that have been peer-reviewed within the scientific community or via non-peer reviewed written communications (conference proceedings, books, internet sites). Data from different sources may be helpful in confirming the degree of scientific agreement or uncertainty on a particular point.

In most cases, data need to be extracted from sources that are not intended for that specific purpose. Consequently, data may not be readily available in the exact form or detail required for the risk assessment. At this point, meta-analysis can be considered as a useful tool for combining or pooling the data from different sources in a structured way. In building up the risk assessment model, separate meta-analyses can be carried out to model the overall effect of certain processing stage or intervention strategy on likelihood/concentrations of a pathogen, as well as likelihood/concentrations of a pathogen at a starting point of the model or at any particular point in the food chain (Gonzales-Barron *et al.*, 2017). Multilevel meta-analysis models that account for the effect of selected *moderators* can also be used. For example, in Prado-Silva *et al.* (2015), such models were developed to summarize the effects of sanitizing treatments on *Salmonella* spp., *Escherichia coli* O157:H7 and *Listeria monocytogenes* in fresh produce, as affected by type of sanitizer and washing time and temperature.

Risk assessors familiar with meta-analysis techniques may conduct meta-analysis on summary statistics or on raw data. Original data may need to be requested from authors when the data are critical for a risk assessment. Human resources and availability of sufficient primary research sources will constrain the use of meta-analysis.

Scientific publications often give a good level of detail about the subject matter being investigated. The conditions under which the data were obtained, and the methods used are often well documented. If a number of individual studies addressing the same research question have been found, meta-analysis can be conducted to obtain a more reliable and representative overall estimate.

However, a drawback of published research is that, in many cases, aggregate data rather than raw data are published and that raw data may be difficult to access. Some journals are encouraging authors to make their raw data available, e.g. International Journal of Food Microbiology. The diversity in languages used for publications can pose a barrier to general access and use. Uncertainty and variability in the data are generally not described, and authors might need to be consulted to

obtain information on those aspects. Some research may be published but hard to locate due to a lack of readily accessible computer listings for items like fact sheets, conference proceedings, theses, dissertations, etc.

Another potential downside of published research is the potential for publication bias. This type of bias occurs because publishers prefer to publish novel research findings, rather than confirmatory research. As a result, the reported effects, e.g. for the efficacy of an intervention, may be larger than what might be expected in general and this type of 'error' has been referred to as a *Magnitude Error (M-Error)* by Gelman and Carlin (2014). Publication bias directly affects meta-analysis, although there are procedures to adjust the meta-analytical estimates when publication bias is likely to be present (Rothstein, Sutton and Borenstein, 2006).

10.1.1 *Analytical epidemiological studies*

Epidemiological surveys concern studies that have been commissioned to specifically investigate the causal relationship between the occurrence of foodborne illness and exposure to certain microbiological hazards through food consumption. They are most commonly undertaken as part of outbreak investigations, e.g. case-control or cohort study. These studies can be useful for hazard identification and characterization.

Strength

Epidemiological studies are very specific and provide a large amount of detailed information on the hazard and the consumer group investigated.

Limitations

Data are often generated for a relatively small number of consumers, and thus are not representative of larger consumer groups.

10.1.2 *Microbiological studies of prevalence and counts/concentrations*

The microbiological studies discussed here refer to studies reporting the prevalence and count/concentration of target microorganisms at various stages and those studies reporting the change in these, such as the efficacy of a processing intervention. These studies may report findings throughout the production and processing chain, including in the final food product. They are especially useful for the exposure assessment but may also inform the hazard identification.

Strength

Results from those studies provide useful information as the initial input or data needed for connecting the parts of the exposure model (e.g. Figure 5). Microbiological surveys undertaken at retail can provide valuable data to verify that the exposure model prediction (up to the retail stage) are comparable with what is observed at retail, i.e. a reality check.

For studies related to interventions (or growth or survival) the processing conditions such as durations, temperatures, etc are often reported and these provide useful inputs into predictive microbiological models.

Limitations

These studies often present results in an aggregate form, e.g. mean and standard deviation. Where possible, the raw data, without identifying information, should be requested from the authors as this will allow more detailed interrogation of the data than may be presented in a scientific publication. This allows statistical distributions of the data to be better ascertained and summary statistics (including variances) to be calculated and assessed for different components of the study. Such

intricacies may not be included in the scientific publication, possibly because the data were not specifically collected for use in a risk assessment.

It often happens that different laboratories use different microbial testing methods that are not measuring the same feature. Therefore, when reviewing published articles investigating the same research question, comparability of results should be appraised to see if these sources are in effect measuring the same thing or not, and if so, whether the same level of uncertainty exists. Differences in testing method comparability are probably the most difficult to resolve when attempting to compare final estimates. Ensuring that internationally validated microbiological methods are used can facilitate this comparison. For example, in some tests, different laboratories may use methods with different detection limits. Nevertheless, there have been advances to take into account the limit of detection and/or quantification when analysing data, without having to resort to biased 'substitution' methods (Shorten, Pleasants and Soboleva, 2006; Lorimer and Kiermeier, 2007; Gonzales-Barron *et al.*, 2010; Busschaert *et al.*, 2011; Williams and Ebel, 2014).

10.1.3 *Cross-contamination data during food processing*

The potential for microbial cross-contamination within the food processing environment is well recognized. Data and models that give insight into the extent to which this occurs is therefore required. Important areas will include, for instance, the level of contact between live and slaughtered animals or between raw and processed vegetable material, worker hygiene, operating equipment, plant design, sanitation protocols, and methods of packaging (Gallagher *et al.*, 2016; Pouillot *et al.*, 2015a; e.g. Zoellner *et al.*, 2019).

Strength

These studies can provide quantitative information on the frequency, extent and type of cross-contamination event that occur in a food processing environment. This allows better modelling of the cross-contamination as part of exposure assessment.

Limitations

Due to the amount of time involved in observing a reasonable number of cross-contamination events, and the variability between observation times (e.g. days or shifts), these types of studies likely involve only one or, a few different, food processing environments. Consequently, the results may be specific to the environment that has been observed and may not be representative of the industry as a whole.

10.1.4 *Food handling and preparation*

Storage and preparation practices, both in the home and in the catering environment, can influence the level of exposure. In particular, hazard growth or reduction may occur during storage prior to preparation if the temperature favours either of these processes; reduction in hazard contamination may occur as a result of cooking; and hazard concentration in cooked products may increase due to cross-contamination. To address these issues, data should be accompanied by descriptions of relevant details such as: times and temperatures of storage; typical handling practices and the potential cross-contamination events that could occur during preparation; the extent to which these events occur and the likely numbers of organisms transferred to different locations within the kitchen; the extent to which consumers are exposed to the organisms that are transferred; and typical cooking times and temperatures. Predictive microbiology models will be needed for these stages as well to assess potential changes in levels of pathogens and the resultant effect on risk.

Research has been undertaken on consumer practices, although the work tends to be product and situation specific (e.g. DeDonder *et al.*, 2009; Kosa *et al.*, 2015). As a result, still relatively little

information exists on food handling practices in the home that affect the safety of foods, although this situation is gradually changing (Murray *et al.*, 2017; Young *et al.*, 2017a). Food handling practices vary by geographical region or even within the same country, based, for example, on ethnicity, gender and education. Consumer storage times, extent of cross-contamination, cooking times and temperatures (such as reported by EcoSure, 2008), hot holding temperatures and times, and other data are not generally available. Likewise, relatively little information is available about food handling practices by restaurant and food service operations, including street food, which accounts for an increasingly greater proportion of meals in many countries, and this data gap is also gradually being addressed (Pichler *et al.*, 2014; Samapundo *et al.*, 2015; Tessema, Gelaye and Chercos, 2014). Some research is now being undertaken using human volunteers who are asked to prepare specific foods in custom kitchen that allow observation and video recording of the study participants, so that food handling practices can be quantified and objectively evaluated against prespecified criteria.

Strength

Directly observing food handling practices and measuring food storage, cooking or associated metrics (e.g. temperature) are more reliable than information obtained through an interview. That is, observation allows recording of what people do, rather than what they say they do.

Recording video footage of food preparation is also a good way to reduce researcher bias. The actual food handling practices can be assessed "blindly" through an independent third-party. However, care must be taken that the specific practices that are assessed have been well described and documented to ensure consistency.

Limitations

It is difficult to observe food handling practices directly as they are practiced in homes and food service operations, especially when researchers want to capture video footage of the food handling. The best alternative is to use purpose-built food preparation kitchens that allow observation. However, these are costly to establish and to maintain (including the qualified staff to undertake studies).

These types of studies can pose ethical problems and because they cannot be undertaken in a 'blind' way, i.e. volunteers know that they are being observed, may change the way the food is handled.

Where measurements are involved (e.g. EcoSure, 2008) care must be taken that equipment is properly calibrated and that raw data are critically checked for recording errors.

10.1.5 *Human volunteer feeding studies*

The most obvious means for acquiring information on dose-response relations for foodborne and waterborne pathogenic microorganisms is to expose humans to the disease agent under controlled conditions. There have been a limited number of pathogens for which feeding studies using volunteers have been carried out. Most have been in conjunction with vaccine trials. Examples of the use of volunteer studies to develop dose-response models for a range of enteric pathogens are provide by Teunis *et al.* (1996), which includes references to the original experimental studies.

These studies are generally conducted only with primarily healthy individuals between the ages of 18 and 50, and thus do not examine the segments of the human population typically most at risk. Pathogens that are life threatening or that cause disease only in high-risk subpopulations are not amenable to volunteer studies. Typically, the studies investigate a limited number of doses with a limited number of volunteers per dose. The dose ranges are generally high to ensure a response in a

significant portion of the test population, i.e. the doses are generally not in the region of most interest to risk assessors.

The process of (self-)selection of volunteers may induce bias that can affect interpretation of findings. Feeding studies are not a practical means to address strain virulence variation. The choice of strain is therefore a critical variable in such studies. Most feeding studies use only rudimentary immunological testing prior to exposure. More extensive testing could be useful in developing susceptibility biomarkers.

Usually, feeding studies involve only a few strains, which are often laboratory domesticated or collection strains and may not represent wild-type strains. In addition, the conditions of preparation immediately before administration are not usually standardized or reported, though these may affect tolerance to acid, heat or drying, as well as altering virulence. For example, passage of *Vibrio cholerae* through the gastrointestinal tract induces a hyper-infectious state, which is perpetuated even after purging into natural aquatic reservoirs. This phenotype is expressed transiently, and lost after growth in vitro (Merrell *et al.*, 2002). In many trials with enteric organisms, they are administered orally with a buffering substance, specifically to neutralize the effect of gastric acidity, which does not directly translate into what the dose response would be if ingested in food or water.

Strengths

Using human volunteers is the most direct means of acquiring data that relates an exposure to a microbial hazard with an adverse response in human populations. If planned effectively, such studies can be conducted in conjunction with other clinical trials, such as the testing of vaccines. The results of the trials provide a direct means of observing the effects of the challenge dose on the integrated host defence response. The delivery matrix and the pathogen strain can be varied to evaluate food matrix and pathogen virulence effects.

These studies can provide information on both infection, e.g. by testing faecal matter for the hazard of interest, and illness, e.g. by observing symptoms in the volunteers.

Limitations

There are severe ethical and economic limitations associated with the use of human volunteers; especially because of the ethical implications these studies are no longer undertaken. However, for the purpose of better interpretation and utilization of the data reported in the literature, the aspects that are commonly considered in the development and assessment of an experimental design are listed below.

- What isolate, species, serotype and/or genotype, strain, etc. of the hazard was used?
- How is dose measured (both units of measurement and the process used to measure a dose)?
- How do the units in which a dose is measured compare with the units of measurement for the hazard in an environmental sample?
- Total units measured in a dose may not all be viable units or infectious units.
- Volunteers given repeat doses may not all receive the same amount of inoculum.
- How is the inoculum administered? Does the protocol involve simultaneous addition of agents that alter gastric acidity or promote the passage of microorganisms through the stomach without exposure to gastric acid?

- How is it known that the volunteers are naïve (serum antibodies may have dropped to undetectable levels or the volunteer may have been previously infected with a similar pathogen that may not be detected by your serological test)?
- How is infection defined?
- What is the sensitivity and specificity of the assay used to determine infection?
- How is illness defined?

10.1.6 *Animal studies*

Animal studies are used to overcome some of the logistical and ethical limitations that are associated with human-volunteer feeding studies. There are a large variety of different animal models that are used extensively to understand the hazard, host and matrix factors that affect characteristics of foodborne and waterborne disease, including the establishment of dose-response relations.

Strengths

The use of surrogate animals to characterize microbial hazards and establish dose-response relations provides a means for eliminating a number of the limitations of human-volunteer studies while still maintaining the use of intact animals to examine disease processes. Animal models can be relatively inexpensive, thus increasing the potential for testing a variety of strains and increasing the number of replicates and doses. The animals are generally maintained under much more controlled conditions than human subjects. Immunodeficient animal strains and techniques for suppressing the immune system and other host defences are available and provide a means for characterizing the response in special subpopulations. Testing can be conducted directly on animal subpopulations such as neonates, aged or pregnant populations. Different food vehicles can be investigated readily.

Limitations

A major limitation is that the response in the animal model has to be extrapolated to that in humans. There is seldom a direct relationship between the response in humans and that in animals. Often, differences between the anatomy and physiology of humans and animal species lead to substantial differences in dose-response relations and the animal's response to disease. For a number of food pathogens, it can be challenging to select an appropriate animal model, as the successful extrapolation from the animal to the human population depends on several factors, such as the similarity of pathogenic mechanisms, the physiological and immune responses between animals and humans (Buchanan, Smith and Long, 2000). Several highly effective models (e.g. primates or pigs) can be expensive and may be limited in the number of animals that can be used per dose group; ethical concerns over animal experimentation need to be carefully considered. Some animals used as surrogates are highly inbred and consequently lack genetic diversity. Likewise, they are healthy and usually of a specific age and weight range. As such, they generally do not reflect the general population of animals of that species, let alone the human population. Ethical considerations in many countries limit the range of biological end-points that can be studied.

When human-derived data are absent, the validation of dose-response models built upon animal studies is challenging. However, there are some general considerations regarding animal models to narrow the difference between animal models and human target. When surrogate pathogens or surrogate animal models are used, the biological basis for the use of the surrogate must be clear. Using data obtained with animal models to predict health effects in humans could take advantage of the use of appropriate biomarkers. It is important to use pathogen strains that are identical or closely related to the strain of concern for humans, because, even within the same species and

subspecies, different strains of pathogens may have different characteristics that cause variation in their abilities to enter and infect the host and cause illness.

10.1.7 *In-vitro studies*

In vitro studies involve the use of cell, tissue or organ cultures and related biological samples to characterize the effect of the hazard on the host. They are of most use for qualitative investigations of pathogen virulence but may also be used to evaluate in detail the effects of defined factors on the disease process. For example, the effect of food processing and preservation conditions on a pathogen's virulence and toxin production can be evaluated by *in vitro* studies (Greppi and Rantsiou, 2016; Haddad *et al.*, 2018).

Strengths

In vitro techniques can readily relate the characteristics of a biological response with specific virulence factors (genetic markers, surface characteristics and growth potential) under controlled conditions. This includes the use of different host cells or tissue cultures to represent different population groups, and manipulation of the environment under which the host cells or tissues are exposed to the pathogen, to characterize differences in dose-response relations between general and special populations. In vitro techniques can be used to investigate the relations between matrix effects and the expression of virulence markers. Large numbers of replicates and doses can be studied under highly controlled conditions.

These techniques can be used to readily compare multiple species and cell types to validate relationships between humans and surrogate animals. They are particularly useful as a means of providing information concerning the mechanistic basis for dose-response relations.

Limitations

The primary limitation is the indirect nature of information concerning dose-response relations. One cannot directly relate the effects observed with isolated cells and tissues to disease conditions that are observed within intact humans, such as the effect of integrated host defences. To compare with humans, there is need for a means to relate the quantitative relations observed in the in vitro system to those observed in the host. For many organisms, the specific virulence mechanisms and markers involved are unknown, and may vary between strains of the same species.

Similar to some other data types, such as public health surveillance, these types of studies are usually limited to providing details of factors affecting dose-response relations and to augmenting the hazard characterization but are unlikely to be a direct means of establishing dose-response models useful for risk assessments.

10.1.8 *Biomarkers*

Biomarkers are measurements of host characteristics that indicate exposure of a population to a hazard or the extent of adverse effect caused by the hazard. Examples include serological assays, counts of subsets of white blood cells and production of gaseous oxides of nitrogen. Biomarkers are generally minimally invasive techniques that have been developed to assess the status of the host. Also 'omics' (transcriptomics, metabolomics) type biomarkers can be used (Haddad *et al.*, 2018). The United States National Academy of Science has classified biomarkers into three classes (NRC, 1989; Slikker Jr., 2018), as follows:

- Biomarker of exposure – an exogenous substance or its metabolite, or the product of an interaction between a xenobiotic agent and some target molecule or cell, that is measured in a compartment within an organism.

- Biomarker of effect – a measurable biochemical, physiological or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease.
- Biomarker of susceptibility – an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance.

Even though this classification was developed against the background of risk assessment of toxic chemicals, these principles can be useful in interpreting data on microbial hazards. In future also the gut microbiome might be related to disease susceptibility.

Strengths

These techniques provide a means of acquiring biologically meaningful data while minimizing some of the limitations associated with various techniques involving human studies. Typically, biomarkers are measures that can be acquired with minimum invasiveness while simultaneously providing a quantitative measure of a response that has been linked to the disease state. As such, they have the potential to increase the number of replicates or doses that can be considered, or to provide a means by which objectivity can be improved, and increased precision and reproducibility of epidemiological or clinical data can be achieved. Biomarkers may also provide a means for understanding the underlying factors used in hazard characterization. A biomarker response may be observed after exposure to doses that do not necessarily cause illness (or infection). Lefkowitz *et al.* (1992) noted antibodies to *Vibrio vulnificus* in shellfish industry workers. Biomarkers can be used either to identify susceptible populations or to evaluate the differential response in different population subgroups. Egorov *et al.* (2018) noted the application of salivary immunoassay in a prospective community study of waterborne infections.

It should also be noted that the most useful biomarkers are linked to illness by a defined mechanism, that is, the biological response has a relationship to the disease process or clinical symptom. If a biomarker is known to correlate with illness or exposure, then this information may be useful in measuring dose-response relationships, even if the subjects do not develop clinical symptoms. Biomarkers such as these can be used to link animal studies with human studies for the purposes of dose-response modelling. This is potentially useful because animal models may not produce clinical symptoms similar to humans. In which case, a biomarker may serve as a surrogate end-point in the animal.

Limitations

Biomarkers are often indicators of infection, illness, severity, duration, etc. As such, there is a need to establish a correlation between the amplitude of the biomarker response and illness conditions. Biomarkers primarily provide information on the host status, unless protocols are specifically designed to assess the effects of different pathogen isolates or matrices.

The only currently available biomarkers for foodborne and waterborne pathogens are serological and salivary assays. The main limitation for such assays is that, in general, the humoral immune response to bacterial and parasitic infections is limited, transient and non-specific. For example, efforts to develop an immunological assay for *Escherichia coli* O157 infections have shown that a distinctive serological response to the O antigen is seen typically in the most severe cases, such as those with bloody diarrhoea, but can be absent in less severe cases, such as cases with blood-less diarrhoea. In contrast, serological assays are often quite good for viruses.

Another limitation is that some biomarkers, such as serological assays, can result in false positives. For serological assays, the presence of antibodies that cross-react with microbial antigens used in

the assay or interfering substances that interact with assay components can also lead to false-positive results. Thus, positive Immunoglobulin M (IgM) assay results require cautious interpretation – consideration of clinical course compatibility and epidemiological factors – and/or confirmation by other serological or molecular testing methods (Woods, 2013).

Other biomarkers, such as counts of subsets of white blood cells or production of gaseous oxides of nitrogen are possible but have not been tested extensively in human populations.

10.2 National and international surveillance data

10.2.1 *Food safety rapid alert systems*

A food safety rapid alert system allows national food and feed control authorities to share information about measures taken in response to serious risks detected in relation to food, and as such can provide useful information for hazard identification. This exchange of information helps countries to act more rapidly and in a co-ordinated manner in response to health threats caused by food. One example of a food safety rapid alert system is the *European Rapid Alert System for Food and Feed*[11] (RASFF). Through the RASFF consumers' portal, the latest information on food recalls, public health warnings and border rejections in all EU countries can be accessed.

The functioning principle of the RASFF is simple: if a member of the network has any information relating to the existence of a direct or indirect risk to human health deriving from food or feed, that information must be immediately notified to the Commission and, where the EFTA States are involved, to the Authority. The Commission disseminates this information immediately to all members of the network.

Strengths

This system enables data sharing between geographically linked parties in an efficient manner. The data should be representative of the food within a diverse but geographically linked region.

Limitations

The system is only as good as it's least active member. If one country does not have the resources or expertise to easily contribute data, then the resulting dataset is limited or skewed toward the other countries in the system.

Similarly, the system will likely have good information about common and well recognized hazards, which tend to be part of national surveillance activities or outbreak investigations (Sections 10.2.1 and 10.2.3). Emerging hazards, those that are not actively surveyed or those that do not require reporting under a national health system may be less likely to be captured in a rapid alert system, unless a large enough outbreak has been identified and reported.

While rapid alert systems can be excellent sources of information for when a hazard has been identified in a food, they usually do not provide useful information about prevalence of the hazard occurring. This is because to the denominator is not generally captured and information about the food units in which a hazard has not been detected are not reported. In addition, if a hazard has not been reported for a particular food product in a rapid alert system, then this does not imply that the hazard does not occur in that food – it simply means that the hazard:food combination has not be

[11] https://ec.europa.eu/food/safety/rasff_en accessed 20 June 2019

reported in the system, either because the food has not been tested for the hazard, or because the hazard has not (yet) been detected in the food.

10.2.2 *Outbreak data*

When there is a common-source outbreak of foodborne or waterborne disease of sufficient magnitude, an epidemiological investigation is generally undertaken to identify the cause of the problem, to limit its further spread, and to provide recommendations on how the problem can be prevented in the future. Such information can be particularly valuable for hazard identification and characterization.

An outbreak of confirmed aetiology that affects a clearly defined group can provide very good information about the range of illness that a pathogen can cause, particular behaviour or other host characteristics that may increase or decrease the risk, and – if there is clinical follow up – the risk of sequelae. When the outbreak is traced to a food or water source that can be quantitatively cultured under circumstances that allow the original dose to be estimated, the actual dose-response can be estimated. Even when that is not possible, dose-effect relations can often be observed that show variation in clinical response to changes in relative dose and is part of the classic approach to an outbreak investigation. This may include looking for higher attack rates among persons who consumed more of the implicated vehicle but may also include variation in symptom prevalence and complications. There are good public health reasons for gathering information on the amount of the implicated food or water consumed. An outbreak that is characterized by a low attack rate in a very large population may be an opportunity to define the host-response to very low doses of a pathogen, if the actual level of contamination in the food can be measured. In addition, data from outbreaks are the ultimate "anchor" for dose-response models and are an important way to validate risk assessments (see also Section 16.2.2).

In general, information on several outbreaks– including the dose and the attack rate – is needed to establish a dose-response model, as each outbreak essentially contributes one data point to which the dose-response model is fitted. Examples include the dose-response models for *Salmonella* (FAO/WHO, 2002a) and *E. coli* O157:H7 (Strachan *et al.*, 2005).

Strengths

An outbreak investigation can capture the diversity of host response to a single pathogenic strain, down to the DNA level, e.g. using whole genome sequencing (e.g. Smith *et al.*, 2019). This can include the definition of the full clinical spectrum of illness and infection, if a cohort of exposed individuals can be examined and tested for evidence of infection and illness, e.g. using a case-control study. This may be undertaken independent of whether they were ill enough to seek medical care or diagnose themselves. It also includes definition of subgroups at higher risk, and the behaviour, or other host factors, that may increase or decrease that risk, given a specific exposure. Collecting information on underlying illness or pre-existing treatments is routine in many outbreak investigations.

Obtaining highly specific details of the food source and its preparation in the outbreak setting is often possible, because of the focus on a single food or meal, and may suggest specific correlates of risk that cannot be determined in the routine evaluation of a single case. Often, the observations made in outbreaks suggest further specific applied research to determine the behaviour of the pathogen in that specific matrix, handled in a specific way. For example, after a large outbreak of shigellosis was traced to chopped parsley, it was determined that *Shigella sonnei* grows abundantly on parsley left at room temperature if the parsley is chopped, but does not multiply if the parsley is

intact (Wu *et al.*, 2000). Such observations are obviously important to someone modelling the significance of low-level contamination of parsley.

Where samples of the implicated food or water vehicle can be quantitatively assayed for the pathogen, in circumstances that allow estimation of the original dose, an outbreak investigation has been a useful way to determine the symptoms associated with a defined dose in the general population.

Follow-up investigations of a (large) cohort of cases identified in an outbreak may allow identification and quantification of the frequency of sequelae, and the association of sequelae with specific strains or subtypes of a pathogen.

If preparations have been made in advance, the outbreak may offer a setting for the evaluation of methods to diagnose infection, assess exposure or treat the infection.

Limitations

The primary limitation is that the purpose and focus of outbreak investigations is to identify the source of the infection to prevent additional cases, rather than to collect a wide range of information. The case definitions and methods of the investigation are chosen for efficiency, and often do not include data that would be most useful in a hazard characterization and may vary widely among different investigations. The primary goal of the investigation is to quickly identify the specific source(s) of infection, rather than to precisely quantify the magnitude of that risk. Key information that would allow data collected in an investigation to be useful for risk assessments is therefore often missing or incomplete. Estimates of dose or exposure in outbreaks may be inaccurate because:

- It was not possible to obtain representative samples of the contaminated food or water.
- If samples were obtained, they may have been held or handled in such a way, after exposure occurred, as to make the results of testing meaningless. For example, microbial growth may have occurred if food is held at room temperature for extended periods.
- Laboratories involved in outbreak testing are mainly concerned with presence/absence, and they may not be conducting enumeration testing.
- It is very difficult to detect and quantify viable organisms in the contaminated food or water, e.g. viable *Cryptosporidium* oocysts in water or norovirus in oysters.
- Estimates of amount consumed by infected (and not infected) individuals, and of the variability therein, are poor.
- There is inadequate knowledge concerning the health status of the exposed population, and the number of individuals who consumed food but did not become ill (a part of whom may have developed asymptomatic infection, whereas others were not infected at all).
- The size of the total exposed population is uncertain.

In such instances, use of outbreak data to develop dose-response models generally requires assumptions concerning the missing information. Fairly elaborate models may be necessary to reconstruct exposure under the conditions of the outbreak. If microbiological risk assessors and epidemiologists work together to develop more comprehensive outbreak investigation protocols, this should promote the collection of more pertinent information. This might also help to identify detailed information that was obtained during the outbreak investigation but was not reported.

Even when all needed information is available, the use of such data may bias the hazard characterization if there are differences in the characteristics of hazard strains associated with

outbreaks versus sporadic cases, see for example Frank *et al.* (2014). The potential for such bias may be evaluated by more detailed microbiological studies on the distribution of growth, survival and virulence characteristics in outbreak and endemic strains.

Attack rates may be overestimated when they are based on signs and symptoms rather than laboratory-confirmed cases. Alternatively, in a case-control study conducted to identify a specific food or water exposure in a general population, the attack rate may be difficult to estimate, and may be underestimated, depending on the thoroughness of case finding.

The reported findings depend strongly on the case-definition used. Case definitions may be based on proximity in time and geography, clinical symptoms, on laboratory data or a combination thereof. The most efficient approach could be to choose a clinical case definition and validate it with a sample of cases that are confirmed by laboratory tests. This may include some non-specific illnesses among the cases. In investigations that are limited to culture-confirmed cases, or cases infected with a specific subtype of the pathogen, investigators may miss many of the milder or non-diagnosed illness occurrences, and thus underestimate the risk. The purpose of the outbreak investigation may lead the investigators to choices that are not necessarily the best for hazard characterization.

While outbreaks can be a valuable source of information for hazard identification and characterization, an outbreak ultimately only provides one data point – a combination of dose and estimated proportion of infected or ill persons. Consequently, numerous outbreaks involving the hazard (though possibly different strains) are required to allow the fitting of a dose-response model.

10.2.3 *Foodborne disease surveillance and annual health statistics*

Countries and several international organizations compile health statistics for infectious/zoonotic diseases, including those that are transmitted by foods and water. The data included in many cases are very specific, with rather detailed descriptions of the food (e.g. type, amount, composition), pathogen (reliably identified, often subtyped) and consumer (e.g. age, gender, health condition) being collected, often in the pursuit of identifying and investigating outbreaks (see also Section 10.2.1). Enhanced surveillance networks have in recent years improved the accumulation of data generated in foodborne disease investigations. These include Foodnet[12], Pulsenet[13] and Pulsenet International[14]. Such data are critical to adequately identify and characterize microbial hazards in specific food products.

In cases where no surveillance data or health statistics are available, it may be possible to use surrogate sources, if they are available. For example, for infections involving *Taenia saginata* sales data of taenicidal drugs have been used as an indication of the public health burden (Dorny and Praet, 2007).

Strengths

Active public health surveillance for foodborne illness can provide useful information about different disease endpoints and their proportional likelihood. Depending on the amount of information available different estimates may be obtained for various subpopulations of interest. However, care must be taken to account for the effect of under-reporting, which, depending on the hazard, may be substantial (e.g. Hall *et al.*, 2008; Scallan *et al.*, 2011).

[12] http://www.cdc.gov/foodnet/ accessed 20 June 2019
[13] http://www.cdc.gov/pulsenet/ accessed 20 June 2019
[14] http://www.pulsenetinternational.org/ accessed 20 June 2019

Annual health statistics provide one means of both anchoring and validating dose-response models (see Sections 16.2.2 and 16.2.3). The effectiveness of dose-response models is typically assessed by combining them with exposure estimates and determining if they approximate the annual disease statistics for the hazard; this process is sometimes referred to as a 'reality check.'

In addition, surveillance statistics may provide useful information about different morbidity ratios, i.e. rates with which different severities are observed. For example, Scallan *et al.* (2011) provide information on hospitalization and mortality rates and these differ between hazards or between different countries/regions (WHO, 2015). Similarly, surveillance information together with microbiological and genomic analyses can support the understanding of the severity of a hazard, e.g. some STEC strains have greater potential to cause more severe illness (from diarrhoea, bloody diarrhoea to haemolytic uremic syndrome) illness than others (FAO/WHO, 2018a).

In addition, annual disease statistics data have been used in conjunction with food survey data to rapidly estimate a simple dose-response relationship. It must be noted that, usually, analysis of such aggregated data requires many assumptions to be made, which increases the uncertainty in the results. This approach is highly cost–effective since the data are generated and compiled for other purposes. Available databases often have sufficient detail to allow consideration of special subpopulations.

Limitations

The primary limitations of these data are that they are highly dependent on the adequacy and sophistication of the surveillance system used to collect the information; and data only concern a limited range of microbiological hazards and do not necessarily reflect sporadic cases. Typically, public health surveillance for foodborne diseases depends on laboratory diagnosis. Thus, it only captures those who were ill enough to seek care (and were able to pay for it), and who provided samples for laboratory analysis. This can lead to a bias in hazard characterizations toward health consequences associated with developed nations that have an extensive disease surveillance infrastructure. Within developed countries, the bias may be towards diseases with relatively high severity, that more frequently lead to medical diagnoses than mild, self-limiting diseases. Comparisons with other countries are difficult because a set of defined criteria for reporting is lacking at an international level.

Another major limitation in the use of surveillance data is that it seldom includes accurate information on the attribution of disease to different food products, on the levels of disease agent in food and the number of individuals exposed. Use of such data to develop dose-response relations is also dependent on the adequacy of the exposure assessment, the identification of the portions of the population actually consuming the food or water, and the estimate of the segment of the population at increased risk. Nevertheless, these national surveillance data have been used in combination with national production or consumption data to provide crude comparisons across commodities (Hsi *et al.*, 2015).

10.2.4 *Systematic food contamination monitoring surveys*

Frequently, governments have set up proactive programmes to sample food and water for the occurrence of microbiological hazards of concern, which can be determined as a percentage of contaminated samples (the prevalence) and/or the number of microorganisms, e.g. CFU/gram of food. In addition, governmental agencies (inspection and control services, or assigned laboratories) carry out routine surveillance monitoring. Such data can be useful for hazard identification and also for exposure assessment or risk assessment. Most pathogen testing is presence/absence testing, because of the low expected contamination, and usually involves sample enrichment to allow the

target organism to grow enough to improve detection. Thus these tests are non-enumerative, unless multiple samples are tested in which case the proportion of samples that become positive can be used to estimate the concentration, similar to the Most Probable Number (MPN) method (e.g. Kiermeier *et al.*, 2011). There are some hazards for which tests do not yet exist, so even prevalence data may not be easily obtained. For example, until relatively recently, no reliable diagnostic tests were available for norovirus. This situation has now been addressed using molecular methods, though it still is not yet possible to differentiate between infective and non-infective virus particles (e.g. DNA fragments and damaged capsid). Finally, it should be noted that the efficacy of testing frequently depends on the size of the analytical unit tested, e.g. 1g versus 25g (Funk, Davies and Nichols, 2000; Vimont *et al.*, 2005).

In many of the exposure assessments published to date, the lack of specific data on primary production has often been identified as a weakness. Occasionally, governments or other stakeholders arrange programmes that specifically survey establishments involved in primary production. However, such programmes are often run for other purposes, e.g. to better understand pathogen ecology and production hygiene with the aim of improving or refining control measures when necessary. Such studies are often small, specific studies that typically concern one hazard and one commodity type (e.g. *Salmonella* in broiler chickens), which may nevertheless be enough for a specific risk assessment.

If national data on foodborne pathogens are not systematically collected in a country or region, it may be possible to utilise data from another country. In that case, the rationale for the choice of country and information on the possible limitations of the data in representing the current situation in the country in question need to be clearly documented.

Strengths

These activities generate substantial amounts of data, both in the form of prevalence or contamination level information. The potential for the use of such data in exposure assessments should be good, especially for systematic monitoring that covers a wide range of products in a certain category and a significant area (a country or region). To allow optimal evaluating of data on prevalence and level of contamination, proper descriptions of the details (i.e. year, season, geographical location, country, etc.) should be provided.

Limitations

Surveillance data collected by different government agencies are rarely pooled and the raw data may not be readily available or easy to obtain. Also, a detailed description of the product or hazard may not be provided. Additionally, a major drawback is that these data may not be random or fully representative. They are generated as part of official control systems that often take account of resource limitations by targeting foods that are known to be problematic. Alternatively, they are generated to support food inspection processes where samples are only taken if there appears to be something wrong with the hygiene of the premises or process, hence these data are often biased. In many cases, the lower (and upper) limit of detection (LoD) and analytical unit size are not reported, and neither are the sensitivity and selectivity (or specificity) of the detection method(s) utilized. Surveillance data collected at both primary production and processing/retail have a clear limit in terms of geography and time.

10.2.1 *National food production statistics*

Food production statistics provide an estimate of the amount of food commodities available to the total population, and as such can be useful for exposure assessment. Examples of this type of data

include the FAO Food Balance Sheets (FAOSTAT[15]) and other national statistics on total food production, disappearance or utilization. Because these data are available for most countries and are compiled and reported fairly consistently across countries, they can be useful in conducting exposure assessments at the international level.

Strengths

These reports contain detailed information and provide a good overview of a country's production of food commodities and imports.

Limitations

Figures reported may be outdated and for some food commodities, production statistics may not be available. It is important to note that production statistics are not necessarily specific to how much of the product is destined for the food supply as compared to other uses, e.g. biofuels. In addition, total amounts of a commodity may need to be adjusted to account for spoilage or other losses to arrive at the total amount that is consumed as food.

A 'reality check' relating food consumption to food production should be undertaken where possible. That is, if food consumption statistics are available and they are aggregated over the whole population, does the total amount of the food consumed approximately equal the total production for food, considering imports and exports, (likely) losses during processing and preparation and general wastage? If not, then some of the assumptions underlying the calculations may need to be critically assessed.

10.2.1 *National consumption databases*

Two types of food consumption data are frequently used for characterizing food consumption patterns for MRAs: food production statistics and food consumption surveys. These data can be very useful in exposure assessments. Other sources of information such as retail food sales or purchase data may be useful in filling data gaps in either food production or food consumption survey data. When using such data, allowance should also be made for the effects of food wastage and food spoilage.

Some countries have carried out Food Basket studies to describe the amounts and frequency of foods consumed. In countries where household food surveys have been carried out, useful information for exposure assessments might be available. In addition, the use of 'Participatory Epidemiology' methods (Mariner and Paskin, 2000) could be of value in data collection as well, being based on participatory techniques for gathering information based on community observations and traditional oral history (Bergold and Thomas, 2012).

Another data source of potential use is the WHO GEMS/Food consumption database[16]. This database provides information for a total of about 500 items at up to three levels of statistical food categorization on a country/cluster basis. These data may provide a useful starting point, though care needs to be taken with respect to interpreting the results. Where possible data should be checked against other sources.

Food consumption patterns will probably differ based on population demographics (age, gender, ethnicity, health status, socioeconomic group) and seasonal and regional (both national and international) differences in food availability. Consideration of food consumption patterns for sensitive subpopulations (e.g. young children, pregnant women, the elderly and the

[15] http://www.fao.org/faostat/en/#data accessed 12 July 2019
[16] https://www.who.int/nutrition/landscape_analysis/nlis_gem_food/en/ accessed 10 December 2018

immunocompromised) and high-risk consumer behaviour (e.g. consuming unpasteurized dairy products or undercooked or raw meat products) are particularly important. Information that enables estimation of variability in serving size will also be important.

Strength

Food consumption surveys can provide detailed information regarding the types and amounts of foods consumed by individuals or households and sometimes also the frequency with which the foods are consumed (van Rossum *et al.*, 2011). These surveys usually include a representative sample of individuals or households, from which consumption for the total population or specific population subgroups can be extrapolated. It is possible that food consumption data may be available for the 'at risk' group for a specific area.

When surveys are repeated over time then changes in consumption patterns may be observed.

Since serving size directly affects the numbers of pathogen consumed, these surveys may provide a method to determine a distribution of amounts consumed. Although the surveys are usually short in duration (one or two days to a week for each survey participant or household), they provide detailed information about the types of food consumed, as well as when and where foods are consumed (van Rossum *et al.*, 2011).

Limitations

Food consumption patterns may vary widely within a country and the consumption estimates derived from national food balance sheets will not reflect this variability. For example, in Sub-Saharan Africa the majority of the population live on the land and eat what they produce, though there may be considerable differences in consumption from the population that lives along the coastal areas. National food consumption surveys would be of great value here, but they are conducted in relatively few countries worldwide.

Not all national survey data sets have raw data by time of day and place of consumption as well as a total amount of each food consumed, and even if they do, it is often difficult to extract this type of information and analyse it (e.g. the time of day needs to be clearly defined at the time of the survey, as well as when data are sub-divided for analysis, etc.). It also requires fairly sophisticated software to be able to analyse individual dietary data at this level of detail, as opposed to deriving mean or median population statistics. This is particularly true if all sources of a food are required to be aggregated at an individual person level (e.g. apples from raw apples, apple juice and apple pies). In terms of microbiological risk assessment, this addition of food consumed from different sources also has additional problems as each food source is likely to have a different level of contamination of the hazard due to different food processing and preparation routes.

Food consumption surveys generally do not record descriptive information about the foods that may relate to food safety. For example, they may not report whether milk was raw or pasteurized, whether a soft cheese was made from raw milk, whether cooked shrimp were domestically produced or imported, or whether a food was packaged by the processor or at retail. For this information, food sales data from industry, trade associations, retail stores and other sources can be combined with results of food consumption surveys to estimate the frequency with which very specific food products might be consumed. Whenever possible these data should be compared with information from epidemiological studies (case control, cohort or outbreak investigations) to verify or calibrate that food survey data capture the actual risk factors.

10.2.2 *National population census*

Governments regularly publish reports on population size by region, gender, age strata, etc. These figures may be useful when characterizing the risk at population level and/or by type of population.

Strengths

These reports contain detailed information and provide a good overview of the country's population demographics, including age (possibly group, e.g. 20-25 years, etc,), gender, socio economic status, etc.

Limitations

Reports on population census may be outdated as censuses are very resource intensive and are therefore undertaken relatively infrequently, e.g. every seven or ten years. Care should be taken to ascertain how the census was administered and what sub-groups of the population may not have been captured, e.g. homeless people, and what approaches, if any, have been used to adjust for these.

Population statistics generally do not capture at risk groups, unless they are specifically related to demographic characteristics, e.g. age.

A specific problem for international exposure assessments is that information and data may not be accessible due to language barriers. Both finding relevant data and correctly interpreting their context may be a problem.

10.3 Industry data

Both textual and numerical data can be obtained from industry stakeholders, including occurrence of microbiological hazards, production stages and processing conditions, description of the final product and product pathways. Data on product sales and market share may also be available from private marketing agencies, trade associations and industry. These data are very relevant for the exposure assessment.

Industry can furnish information on whether the product is fresh or frozen, whether it is sold cooked or uncooked, whether or not it is further processed and the extent to which ingredients are mixed. A complete description of the food, including salt levels, pH, packaging and other relevant information should be provided. Such data may also refer to other factors that may influence the prevalence and/or concentration of hazard in the food, e.g. the extent to which the product and sub-products are domestically produced or imported; the different ingredients added; or other products typically consumed with the product.

The food chain consists of all stages from primary production to the consumption (including home, restaurant, foodservice, and/or institutional locations), and thus data relating to each of these stages are required as part of the exposure assessment. Using meat processing and distribution as an example, the various stages will include the farm; transport to and holding at a slaughterhouse or processing plant; slaughter; processing; packaging; storage; distribution and retail; transport to the home; handling and home storage; food preparation; and consumption. Some of these stages and processes may vary between producers, retailers and consumers and thus it is important to obtain information to describe and account for this variation – this is particularly pertinent for exposure assessments where formal and informal supply chains exist. Certain stages or processes may be regulated, for example, with respect to the use of chemicals or additives; such regulation and information on the extent to which they are followed in practice may give relevant data to be collected.

Considering growth and survival of a microbial hazard, the times, temperatures, and other ecological factors such as pH at the various stages are important. Particular examples of requirements include the duration of, and temperature during, storage or transport; freezing temperatures; pasteurization times and temperatures; cooking times and temperatures; and the addition of ingredients that may alter pH. Data that enable description of the variation in these parameters, for example from producer to producer or day to day, are also important. Often, individual stages in the food chain are considered to be static for a specified period. However, certain conditions, such as temperature, are more likely to be cyclic and data should reflect that. While data may be readily available on thermal inactivation, data on other types of thermal or non-thermal processing that affect microbial growth and survival may not be as readily available.

It is also important to gather information relating to the stages of mixing and partitioning. For example, the meat from an individual beef carcass can be partitioned and then perhaps mixed with meat from other beef carcasses to produce a ground beef burger. Partitioning and mixing will influence the microbial status of the product, in terms of both likelihood of contamination and number of organisms, and thus data that are descriptive of these processes should be collected. Typical requirements will include the extent to which both events occur, the numbers of carcasses or products contributing to a mixed product, and characteristics of products obtained through partitioning (including distributions in quantity and size).

Retail surveys also represent another source of industry data, including information on geographical area, season, and the degree to which the data represent all manufacturers, distributors or retailers.

Strengths

Industry collects vast amounts of product/commodity specific data, which it stores in a wide array of private systems. Gaining access to such data and information about product pathways, can provide the risk assessor, and risk manager, with important information about the realities of the food production, that might otherwise not beknow with confidence.

Where sampling, testing and monitoring programs are in place, information will be available over time and at various stages during the production, from supplied raw ingredient through to finished product. Such data will be useful for application of predictive microbiological models when the fate of microorganism is to be predicted.

In some businesses sampling and testing of the raw material and end product is extensive and frequent as it is the primary means of 'ensuring' food safety. Other businesses employ a preventative approach to food safety such as the implementation of a food safety management system based on the principles of HACCP. In these businesses microbiological testing is infrequent and solely for the purpose of verifying the effective working of the HACCP system. Furthermore, the food production environment is sampled due to considerations of cross-contamination

Limitations

Major limitations to the inclusion of industry data in exposure assessments are the facts that they may not be hazard specific and are difficult to combine when generated in industrial settings that are difficult to compare individually. Because sampling and testing is usually done for verification purposes or to satisfy regulatory requirements, the data often concern the presence/absence of a microbiological hazards rather than the levels/concentration. When testing is done for indicator organisms the levels of contamination are usually recorded, but mainly for generic groups of microorganisms, such as total viable counts or Enterobacteriaceae.

In addition, access to and mining (retrieval) of such data is a problem in practice. In this regard, there is also a need to address the issue of confidentiality, which may be a stumbling block in relation to access. The use of proprietary information and data can poses some challenges and how to keep this information and data confidential needs to be discussed and agreed prior to their provision, as is done by FAO/WHO (2018b).

In addition, potential biases need to be considered, especially relating to the difference in processing and food safety programs related to business size. Large manufacturers process on an industrial scale with better and more automated equipment than small food producers. As a result, they can supply more geographically diverse retailers and supermarkets and access a different consumer segment than small food producers who sell their products at informal markets (especially in developing countries).

Similarly, large enterprises are more likely to have food safety programs in place, including spending (more) money on microbiological testing programs. This contrasts with small or very small enterprises, which are less likely to undertake much, or any, microbiological testing. If a food is tested for microbial contamination, anywhere in the food supply chain, then the industry stakeholders should provide sufficient information on the food, microbiological methods, sampling design and frequency of sampling, etc. However, such information may not readily be available.

An important limitation in collecting retail survey data by any group (e.g. trade association, academia, consultant) is that the identification of a contaminated food might trigger a recall (e.g. *Listeria* in a ready-to-eat (RTE) food or *E. coli* O157 in ground beef). This may make such surveys of limited value because any kind of recall may change the foods in distribution and impede future industry cooperation. Alternatively, when such studies are commissioned by industry, there may be a limitation placed on the type of microbial data that is collected, e.g. hygiene indicators and/or presence absence of specific genes rather that direct isolation of the pathogen.

10.3.1 *Description of product and supply chain*

Throughout the food chain, many control options are available to reduce the risk of microbiological contamination of the final food product. These may be incorporated in HACCP plans that are specific for each product and manufacturing site, and thus may vary substantially between manufacturers. Data should be collected that describe both the methods of control and the extent to which these vary. Examples include cleaning and disinfection methods and the extent and frequency with which these are undertaken; inactivation methods and their critical limits; any testing of live animals and intermediate or final products, with estimates for test sensitivity and specificity; and handling practices.

10.4 Unpublished data

Potentially vast amounts of data (generated throughout the world) are never published in a form that can be used by others. This can be due to many different reasons that can for instance relate to the attractiveness of the subject to publishers or the (scientific) community, i.e. publication bias, barriers in communication (resources, language) or due to time and/or resource constraints for the researcher. This is an unfortunate situation; such data could give new insights, reduce uncertainty and avoid unnecessary duplicate experimentation. However, like other data sources, the quality of unpublished data need to be ascertained carefully before use in a risk assessment.

Some steps can be taken towards improving access to such data. Building networks is very important in this regard, as these can be used to inform a wider audience of the data needs for risk assessment and also provide a means of gaining information about, and even access to, unpublished studies.

Building up a relationship with potential data providers is essential in establishing trust and instilling confidence that the data will be used properly and remain confidential if necessary. There is a need for networking, especially with others who might be working in areas where data are required.

Another avenue for gaining access to unpublished data is through public calls for data, which is usually undertaken for international risk assessments by FAO/WHO, as well as national competent authorities. This also forms an important part of risk communication and helps to involve different stakeholders.

10.5 Data gaps

All risk assessments require data and knowledge (of processes, interactions, etc.), irrespective of whether they are qualitative or quantitative. Data and knowledge gaps influence the assessor's confidence in the risk characterization and the robustness of the estimate. The form of a risk assessment is determined primarily by looking at what decision questions need to be answered, taking into account the decision criteria described in Section 3.5. Then a search is done to see what data and knowledge are available that would help construct a logical risk-based argument (the risk assessment) that answers these questions. A balance is generally needed: taking a particular risk assessment approach may not be able to answer all questions but may provide a better-quality answer. Data may not be available to answer the question at all. Thus, defining the form of a risk assessment may require considerable dialogue between assessor and manager.

Both numerical and textual data are required to model all stages of the exposure pathway. Often, data are limited or non-existent. However, a lack of knowledge about a process should not necessarily inhibit the ability to conduct an exposure assessment. When deficiencies in the data exist, they must be clearly communicated to the risk managers and documented in the exposure assessment. Such communication will ensure that additional data requirements are identified. Even in situations where appropriate and representative data are known to exist, problems can still occur. For example, there may be institution or company confidentiality to consider, the data may be politically sensitive or there may be a charge for use of the data. The iterative nature of risk assessment allows for the continuous upgrading of data as new information becomes available.

This process will often lead to a better understanding of the value of other information that is not currently available. One can ask what else could be done if some specific data could be found. Depending on the time left until a decision has to be made, and on the resources available, the risk manager may consider it worth waiting, or expending the resources to acquire those data and hopefully be able to make a more informed judgement as a result.

It is tempting to plan out the structure of a risk assessment that will answer all the risk managers' questions, and then attempt to find the data required to 'populate' the risk assessment. However, in the food safety area this may not be a practical approach. Food safety management is beset by a lack of data, so writing a wish list of all the data one would like will inevitably lead to disappointment. Other approaches, such as building simplified model-based reasoning to describe the system or process before considering the data availability (Ebel *et al.*, 2012), have been proposed as preliminary activities to aid in determining the form of the risk assessment. A brief list of reasons for such gaps includes:

- it has not previously been seen to be important to collect these data;
- data are too expensive to obtain;
- data are impossible to obtain given current technology;
- past data are no longer relevant;

- data from other regions are not considered relevant; or
- the data have been collected or reported, or both, in a fashion that does not match the risk assessment needs.

Data that have not previously been seen to be important often arises in contamination studies with infrequent detection data. Such data are not usually valuable for scientific journals; therefore, researchers have less interest in conducting such studies. However, data on non-detections are important for risk assessment, e.g. to estimate prevalence.

Using the risk assessment framework, it may be possible to determine which gaps have the most influence on being able to address the risk management questions. This identification process can be used to set priorities for future data collection and experimental research.

There are a number of approaches that can be used to help overcome limitations in data. These include model design, surrogate data, expert opinion and the collection of new data.

10.5.1 *Model restructuring*

Ideally, all stages in the exposure pathway that affect the hazard are included in the model structure. However, in many situations, data for specific stages may be limited or even non-existent. Also, the statement of purpose for conducting the risk assessment may not require detailed analysis of all processing stages, i.e. a farm-to-fork exposure assessment may not always be required. When this is the case, it may be possible to restructure the model to exclude the stage for which data are not available or in such a way that alternative available data can be used (e.g. beginning the exposure assessment after the processing stage and obtaining prevalence and concentration using monitoring data); clearly any changes in the scope must be discussed and agreed with the risk managers. In addition, simplification of the model may have the benefit of reducing the compounding of uncertainties. There are limitations with this technique, as important factors that have an effect on the risk may be overlooked and lead to errors. Cullen and Frey (1999) provide a useful discussion of trade-offs regarding various levels of model complexity.

10.5.2 *Surrogate data*

In one sense, nearly all data are surrogate data unless specifically collected as part of the exposure assessment. Pilot plant data, for example, is a surrogate for production facilities; thermal death time values obtained via capillary tubes are surrogates for inactivation in the plate pasteurizers used in food processing. Classically, certain benign species or strains of microorganisms are used as surrogates for pathogenic strains. In such cases, the relevant characteristics of the surrogate organisms should be the same as the organism of interest, or the differences documented and taken into account. Surrogate organisms are more appropriate for quantifying or predicting treatment efficacy than for predicting or quantifying health effects such as actual dose-response relationships. The appropriateness of the surrogate data must be judged when assigning uncertainty to the data. For transparency, use of surrogate data must be described and justified.

Indicator microorganisms for particular microbiological hazards have been used in some exposure assessments where data on the hazard is not available or cannot be collected. An example would be the cross-contamination rate of *E. coli* O157:H7 from faeces to animal carcasses. Because of the low prevalence of *E. coli* O157:H7 in faeces, a direct measure of contamination cannot readily be obtained. The easily measured generic *E. coli* is therefore used as an indicator of faecal to carcase transfer, which can then be related back to *E. coli* O157:H7. When using surrogate data, care should be taken to clearly identify where it was used and any underlying assumptions (e.g. proportionality between the pathogen and surrogate) should be explicit whenever possible.

Regarding food consumption data, if there is insufficient detail to provide estimates for at-risk populations (pregnant women, immunocompromised, elderly, etc.), data for comparable age and gender groups in the normal population may be used. Data from other countries or regional data may also be used for food consumption if it is known that food consumption patterns are similar.

Sensitivity analysis (Chapter 15) of the final model can be used to determine if the parameter, for which surrogate data were used, has a significant effect on the final risk. If the parameter is important in estimating the risk, then an additional study may be undertaken to try to collect more relevant data.

10.5.3 *Expert knowledge elicitation (EKE)*

Expert knowledge elicitation is a formal approach to the acquisition and use of expert opinions, in the absence of or to augment available data. It will inevitably be necessary to elicit expert estimates for parameter values in the model where there is a critical lack of data, and where for pragmatic reasons it is essential to assess that risk in the relatively near future. Problems here include, for example, decisions on identification and selection of experts, the number of experts required, techniques for eliciting information, overcoming bias, etc., and methods are still being developed in this area (e.g. Jenkinson, 2005; Hemming *et al.*, 2018; Dias, Morton and Quigley, 2018).

Such expert opinion should be elicited using formalized and documented methods that avoid bias and can be used to formulate appropriate probability distributions (Gallagher *et al.*, 2002; Nauta *et al.*, 2001; Vose, 2008). In situations where expert opinion differs markedly, weighting methods can be used to integrate information in the most reliable manner. Experts should strive to transparently document the rationale supporting their opinion to the greatest extent possible.

When expert opinion is required, the problems and methods of selection, overcoming bias, etc., up to this point are likely to be similar irrespective of the level of quantification used for the risk assessment. It is accepted that ideally a 'sufficient number' of experts should be utilized. Techniques like the Delphi method (Linstone and Turoff, 2002), and modifications such as IDEA (Burgman, 2015; Hemming *et al.*, 2018), which aim to achieve consensus among a panel of experts, can help produce more reliable estimates from the available information. However, there are situations when there truly are very few, and on occasions perhaps only one, expert in the specific topic worldwide. Sometimes there are no true experts. This leads to the use of inputs with very wide levels of uncertainty, whatever the risk assessment type, which is far from ideal but may be the only option in the short term.

In a quantitative risk assessment, it is necessary to convert expert opinion into a numerical input, and once again various methods exist and are being actively developed (e.g. Gallagher *et al.*, 2002; Burgman, 2015; Dias, Morton and Quigley, 2018). Even in a qualitative risk assessment, these methods may be used to convert expert opinion into numerical values for specific model steps and this is, where time allows, the preferred method. As noted earlier, when used to describe approaches to risk assessment, the terms quantitative or qualitative do not refer to formally defined categories of risk assessment. An alternative and less sophisticated way of using expert opinion in qualitative risk assessments, however, may be to ask directly for an opinion on the probability of a specific step in narrative terms of, for example, high, low, negligible, etc. The meanings of these words will have the same subjectivity problems as those discussed for qualitative risk assessments in general (see Section 7.2), and the reader's evaluation of the results will need to be based on their evaluation of the experts selected. In principle, such a method should be only a temporary measure until improved data are available.

The estimation of dose-response model parameters is unlikely to be based on expert elicitation and instead based on model fitting. The choice of dose-response function, that is, the mathematical form, is often based on the modellers' expertise, and thus forms a type of expert opinion. When no dose-response model exists the likely dose needed to result in a specific human health effect, e.g. ID_{50}, may require expert elicitation; especially for emerging hazards that have not been studied extensively.

Readers with further interest in the use of expert opinion should consult Morgan and Henrion (1992), who present a sequence of chapters summarizing the heuristic biases in expert elicitation, a typical formal expert elicitation protocol intended to overcome such biases, and examples. Informal EKE can be performed with less experts without the presence of an experienced facilitator in the sense that a small group of scientists wish to quantify their own knowledge about an uncertain quantity, for the purposes of some scientific endeavour. In any case however, the scientists' judgements should be made as carefully and objectively as reasonably as possible and documented fully, according to the principles of the formal EKE. Additionally, EFSA Guidance on Expert Knowledge Elicitation in Food and Feed Safety Risk Assessment (EFSA, 2014a) and the Intergovernmental Panel on Climate Change (IPCC, 2001) discuss the process of expert elicitation in scientific assessments.

Strengths

When there is a lack of the specific data needed, say, to develop dose-response relations, but there are scientific experts with knowledge and experience pertinent to the elucidation of the information required, expert elicitation provides a means of acquiring and using this information. This can involve the development of a distribution for a parameter in a model for which there is no, little or inconsistent numerical data, through the use of accepted processes that outline the lines of evidence or weight of evidence for generation of the opinion and use of the results. It is generally not expensive, particularly in relation to short-term needs.

Limitations

The results obtained depend on the methodology used and are inherently subjective and thus open to debate. The results also depend on the experts selected and may have limited applicability for issues involving an emerging hazard.

10.5.4 *Collection of new data*

At times the need arises for the collection of new data, e.g. prevalence and concentration data for a foodborne pathogen at a specific point of the food chain. The process of obtaining an estimate of the prevalence or the enumeration of microbiological hazards usually involves the following steps:

1. Define the research question
2. Identify the reference population and study population and obtain an appropriate sampling frame
3. Design a sampling scheme and identify the sample population
4. Collect and analyse appropriate samples
5. Conduct statistical analysis of the data

Those contemplating the collection of new information for use in risk assessments should consult a statistician or someone trained and experienced in data collection, especially someone who is familiar with the underlying research domain, e.g. microbiology, consumer behaviour, etc.

10.6 Recommendations on data collection and organization

The characteristics of the data that might be needed at a particular stage are likely to vary from assessment to assessment. Whilst certain characteristics may be considered ideal, in practice it is often necessary to use, in the first instance, whatever data are available. This brings into focus the iterative nature of a risk assessment, which is concerned with the fact that initial attempts to model a process are likely to utilize data with a high degree of uncertainty. This process can be used to identify where the greatest uncertainty lies, allowing targeted data collection for subsequent model updating. Gradually, with further iterations of the modelling process, the uncertainty is reduced. Thus, the first iteration of the assessment might be undertaken specifically to identify data needs and/or data gaps. The second iteration may assess the risk of exposure, but with wider uncertainty limits; and the third iteration, using 'new' data, may allow an estimate of the exposure with a narrower uncertainty band and higher predictive ability. There may be considerable time delays between these stages. The level of uncertainty should be included in the data description.

10.6.1 *Searching for data*

Search protocols using computer-searchable literature databases and data repositories, such as,

- Promed: http://www.promedmail.org/
- Pubmed: https://www.ncbi.nlm.nih.gov/pubmed/
- ComBase: http://www.combase.cc
- FAOSTAT: http://www.fao.org/faostat/en/
- WHO/GEMS: https://www.who.int/nutrition/landscape_analysis/nlis_gem_food/en/
- FoodRisk.org: http://foodrisk.org/
- Food Science and Technology Abstracts (FSTA): https://www.ifis.org/fsta
- OVID Current Contents: http://www.ovid.com/site/catalog/databases/862.jsp
- Web of Science: https://clarivate.com/products/web-of-science/
- Scopus: https://www.scopus.com/

should be devised that are comprehensive and reproducible but are also appropriately selective. Systematic plans for obtaining literature that predates these databases or that is not indexed in them need to be devised using citations in more recent publications, reviews and book chapters. Criteria for search protocols and data selection should be transparent, with appropriate explanation recorded in the documentation.

The Research4Life resources noted in Section 3.5.2 may be helpful in gaining access to scientifically published articles and associated data.

10.6.2 *Selection of data*

It is frequently stated that 'all data are biased'. Nevertheless, data should be as representative as possible of the food, microbial or process parameters being assessed and the population consuming the food. Preferred data generally comes from peer-reviewed publications, followed in importance by non-reviewed or unpublished data (government documents, theses, proceedings, etc.; see Chapter 10 for details). Some data are not available in the peer-reviewed literature (e.g. consumption data), and it should be remembered that even peer-reviewed data are, in most instances, not collected for the purpose of being used in exposure assessments, and thus may not comply fully with all data requirements or be fully representative for the case at hand. Any biases or limitations in the degree to which data represent any particular point of view should be identified and documented (e.g. funding source). When no or too few data are found, expert opinion will need to be used (see Section 10.5.3). Generally, the data should be as close as possible to, or specific to, the requirements of the exposure assessment. For example, if the exposure assessment were to

calculate the exposure in a particular country, the preferred data would come from that country. The next choice would be data in that region or a comparable country; the final choice would be from somewhere else in the world (keeping in mind the purpose of the risk assessment). Selection criteria should include consideration of factors such as geography, time, microbial strain, methodology, equipment type and design, and population demographics. Food consumption data should provide sufficient detail to allow estimates of consumption of the food(s) of interest per meal or per day. The data should be representative of the total population, and ideally will provide information about subgroups within the population.

10.6.3 *Formatting of data*

The ideal format of the data will vary with the particular type of data required; there is no one ideal format for all data. In particular, data that are descriptive of the biological and manufacturing processes will generally be textual, whereas parameter and model input data would, wherever possible, be numerical.

However, there are some underlying principles that should be considered when formatting data:

- Data should be fully referenced as to source (within the confines of commercial sensitivity).
- Units should be given where appropriate.
- Raw data, rather than average or other summary statistics, should be used wherever possible.
- When raw data are not available, a description of the distribution, the level of uncertainty and the amount of variability should be included to the greatest extent possible.

10.6.4 *Level of detail recorded*

When collecting data for use in an exposure assessment, it is useful to record and report detail to the most complete level available. This should be done in an appropriate way which does not interfere with the flow of the report to the extent that it hampers clear communication. The additional information that describes the data set is often referred to as *metadata*, and there are a number of metadata standards available, though not specifically for microbiological data. Examples of some details that might best be routinely recorded and reported are:

- Information on data source or provenance. This should include: the full reference for the source if a paper or similar; the name of the provider if a personal communication or unpublished data; the date of the collection of the data; affiliation or funding source, or both, of the data provider.
- Information on the study itself. This should indicate whether it was a laboratory- or field-based study.
- Details of sample, including: livestock species (giving scientific name where appropriate) or product definition; source (country, region, category of producer, chain of retailer, etc.); selection method (in particular for livestock, whether samples are clinical cases or random selection); population size; season of collection, if appropriate; portion description or size, if appropriate; and method of collection of samples.
- Information on microbiological methods. This should include: sampling method, microbial species, subspecies, strain, in as much detail as is available (and for pre-specified exposure assessment, the required detail should be specified and collected); tests used, including any variation from published methods; test performance characteristics; units used; and precision of measurement.
- Information on the results obtained. This should be recorded as the raw data, and include: number tested, together with results (including units) given for all samples tested.

10.6.5 *Combining data from different sources*

Representative data are oftentimes limited, and it is often preferable to use all of it. However, decisions need to be made when different data sets have different degrees of applicability and relevance to the parameter being modelled. Techniques such as meta-analysis (Petitti, 2000) can be used for the purpose of combining data sets. Gonzales-Barron et al. (2016) provide an overview on how to integrate prevalence data of pathogens from different sources. More generally, Bayesian approaches (Gelman *et al.*, 2013; Kruschke, 2014) may be useful when considering existing knowledge in the light of recently collected information. In certain situations, using Bayesian techniques allows a better estimate of the parameter to be obtained than if the recent data were used in isolation. When a data set is biased, the data may be adjusted before being combined with other data or used in the risk assessment. An example would be when recent research or methods development demonstrated that data collected by one method consistently underestimated the true parameter value by a known amount.

Weighting is often employed so that data sets considered more relevant have more influence on the estimated parameter value. Weighting by the number of samples is frequently used, so that larger studies have more influence. Weights may also be used to reflect the expert's belief in the quality and appropriateness of the data. Older data or data from another geographical area might be used in estimating the parameter value but be given less weight. The selection of the numerical weighting factors is highly subjective and should be explained for full transparency. Composite data sets may be obtained by averaging, method of moments (Hansen, 1982), or maximum likelihood estimates. Careful examination of the different data sets may facilitate estimates of variation (e.g. different microbial strains used in different studies) or uncertainty (residual errors in statistical analyses). Meta-analysis and mixed-effect models can also be used to evaluate data variation.

To avoid inserting the risk assessor's biases into the parameter values, data should not generally be ignored or deleted. However, certain data sets may clearly be inconsistent with the greater collection of data and knowledge. Comparing the size of the remaining distribution with the divergence of the particular data set may suggest that a particular data set should be excluded. This should be done with caution, as the outlier may indicate another source of variation that is otherwise being overlooked (see Figure 18 in Section 16.1).

10.6.6 *Presentation of data*

The format of the data will affect the method of presentation. The underlying principle is that the presentation should be clear and easy to follow. Again, the data may be textual or numerical. When presenting a large amount of data for a particular exposure assessment, a contents table or list is desirable. An introduction or overview of the assessment puts the data to be presented in context. The data should then be presented in a logical order.

In general, with an exposure assessment, there are one or more pathways by which the consumer may be exposed to the microbiological hazard. The first part of the data to be presented is generally the textual data that describes these pathways. For complex pathways, a high-level overview of the process may be required, followed by a more detailed description for each step in the pathway. Also, graphical presentation of the pathways, such as in the form of a flow chart, is generally helpful.

When presenting numerical data, this should also follow a logical order, and this is again likely to follow the order of the steps in a particular pathway. A tabular format is frequently useful, particularly for raw data. However, enough text should be provided to fully describe the relevance of the data, and how they are utilized in the assessment. Summary data are often also best tabulated. Graphs or histograms may in addition be used to clarify data but should not be used without

explanation. Titles of tables or graphs should allow them to be fully identified and should be unambiguous. References should be clear within the text, diagram or table, and a comprehensive reference list given. Any web pages or similar are probably best attached as appendixes.

11. Quantitative modelling approaches

As introduced in Section 5.2.3 there are different categories of quantitative models. The following categories increase in model complexity and thus also increase in the potential richness of the model outputs. This is achieved by incorporating variability and uncertainty into the model and this allows their effects, and those of the model inputs, on the exposure or risk outputs to be evaluated (see also Chapters 14 and 15).

11.1 Deterministic

Deterministic models assume that inputs to a model are known and fixed values with no variability or uncertainty. Although they are simple models they generally require more data than for a qualitative assessment. A single value, e.g. average, highest level, most often observed value, 95th percentile, etc., is chosen to characterize each input variable in the model such as the concentration in the food; the log reduction from cooking; the amount of food consumed per serving, or the frequency of consumption; etc. The individual point estimates are combined using mathematical models to generate a point estimate of exposure, and, through a dose-response model, the consequent risk. An example of a deterministic model, implemented in a generic framework, is RiskRanger (Ross and Sumner, 2002; Sumner and Ross, 2002). The effects of changes to model variables can then be investigated by 'what-if' testing to generate outputs. For example, the initial scenario may be based on the average for each input variable. Subsequently, however, the difference in the risk estimated from using the most likely value compared to the 95th percentile value, and other scenarios, could be investigated.

When conducting deterministic exposure assessments, selecting a conservative value for each variable has often been used to develop deliberately conservative, 'safe' or 'worst case' estimates. Propagating such conservatism through the model, however, can result in an unrealistic over-estimate of exposure because the exposure estimate can be based on a highly improbable scenario. Thus, a drawback of the deterministic approach is that the likelihood or probability of the estimated exposure actually occurring is unknown. Some values are more likely to occur than others, and without knowledge of the likelihood of each outcome, the risk manager may inappropriately allocate valuable resources to reduce an event that rarely occurs. Stochastic models can overcome this problem.

11.2 Stochastic

The stochastic, or probabilistic, assessment represents all the information available for each input variable, which is described as a probability distribution of possible values. Most parameters such as pathogen prevalence in primary production, pathogen concentration and growth, storage temperatures, serving size, and storage times have a range or distribution of values. These variables are better described as distributions so a realistic range and frequency of values can be represented. In stochastic models, scientific data are used to generate and define probability distributions for each input variable. They are then combined to determine the probability distribution of an adverse outcome (Ruzante *et al.*, 2013). Consequently, the outcome of a stochastic exposure assessment is a statistical distribution that describes both the range of doses of the hazard that might be experienced by an individual or population, and the likelihood of each level of exposure. For example, consider a hazard in a food product.

- The concentration of the hazard in the food prior to heating is log-normally distributed with mean and standard deviation of 1.0 and 0.8 $\log_{10}$ cfu/g and
- The effective reduction from heating the food is also log-normally distributed with mean and standard deviation of 2.5 and 0.7 $\log_{10}$ cfu/g.

Analytically it can be determined that the concentration of the food after heating is also log-normally distributed, with mean 1+(-2.5) = -1.5 $\log_{10}$ cfu/g and standard deviation of $\sqrt{(0.8^2+0.7^2)}$ = 1.06 $\log_{10}$ cfu/g.

However, finding analytical solutions, as above, for a stochastic exposure assessment, often involving numerous stochastic inputs, is usually not possible, particularly if the distributions are not 'Normal'. For this reason, Monte Carlo simulation is usually used to perform the assessment (see below).

The distribution used to describe a data set is dependent on the number and pattern of data points available, and on the knowledge about the nature of the phenomenon or process being modelled. Detailed reviews of the important probability distributions are available in the literature (Cullen and Frey, 1999; Haas, Rose and Gerba, 2014; Morgan, Henrion and Small, 1992; Vose, 2008). Uncertainty in parameter values can also be expressed by probability distributions, as discussed in Chapter 12.

The transition from qualitative assessment to deterministic assessment to stochastic assessment usually represents an increase in both information and time required. However, due to the availability of simulation modelling software, the time involved for a stochastic assessment may not be much greater than for a deterministic analysis. Despite its increased computational complexity over the deterministic approach, much of that complexity is dealt with by the software and the stochastic method is favoured among most risk assessors because it generates more information to support decisions, e.g. by identifying the range of possible exposure levels from all possible exposure routes from which the most likely level of exposure, or any specified percentile value, can be determined. This output provides much greater information than a single point estimate. In addition, stochastic modelling allows for explicit identification, modelling and separation of variability and uncertainty (Chapter 12). However, with the increased complexity also comes the increased risk of introducing errors into the assessment, and the output is more difficult to understand, interpret and use for decisions.

11.3 Monte Carlo simulation

As noted above, stochastic models are generally complex in nature, and as a result are usually difficult, or impossible, to solve analytically. To overcome this problem, the model can be evaluated on a computer, using Monte Carlo simulation. A variety of specialized computer software packages are available to support this approach and are discussed in various texts (e.g. Cullen and Frey, 1999); a good summary is provided in Table 1 of Basset *et al.* (2012). Commonly used programs are spreadsheet add-ons, such as @RISK© and Crystal Ball©. Microbial risk assessors have also used the stand-alone package called Analytica® or the US Food and Drug Administration's web-based, and free to use, FDA-iRISK system (https://irisk.foodrisk.org). Other mathematical (e.g. Matlab) or statistical packages (e.g. SAS, R) can also be used for simulation modelling, including various free add-ons, such as the mc2d package for R (Pouillot and Delignette-Muller, 2010). Models can also be constructed using general-purpose programming languages, including FORTRAN, Python, Visual BASIC or C. Commercial software packages may be less 'flexible' to use compared to programs developed in programming languages by the modeller, although both require specialist expertise to model the processes appropriately. Exchange of models may be hampered if the chosen software is not widely available, and open-source software packages that can be downloaded for free, may help to improve the ability for the risk assessment to be 'audited' by others. Simulation models that can be placed and run on the internet may also be desirable to further facilitate model evaluation (e.g. FDA-iRISK).

To undertake a Monte Carlo simulation, a mathematical model is constructed to describe the exposure assessment, including all variables that influence the exposure and their probability distributions. Collectively, the result of the combined equations is an expression of consumer exposure. The software then evaluates the model by generating, at random, a value for each variable from its corresponding probability distribution. The generated values are then combined according to the mathematical equations that comprise the exposure assessment model, and the exposure is calculated. A single realisation of this generation and calculation process is called an *iteration* of the model and represents the exposure from one possible combination of circumstances. There are many such sets of circumstances, however, some more or less likely than others and leading to greater or lesser exposure. To estimate the full range of possible exposures and the likelihood of each, the simulation software repeats the calculations many times: hundreds of thousands or millions of iterations are commonly performed. The result of each iteration is recorded and the distribution of exposures and probability of each is generated and forms the exposure assessment; intermediate results may also be recorded to provide insights into the model.

11.4 Other model classification schemes

In addition to the classification of models used in quantitative exposure assessment as deterministic or stochastic, other non-mutually exclusive classification 'schemes' might be encountered, *i.e.* the use of one description does not necessarily preclude an additional description from another classification scheme. Several common schemes are mentioned below.

Models can also be categorized as empirical or mechanistic. Empirical models simply describe data or relationships in a convenient mathematical form, without necessarily having an understanding of the underlying biological mechanisms. For example, a smoothing spline (de Boor, 2001) may describe a set of data points adequately, even though there is no biological basis for it. Mechanistic models have theoretical bases formed from the understanding of the behaviour of a system's components, e.g. binary fission bacterial growth. If correctly formulated, then, a mechanistic model should provide a good fit to experimental data and thus allow the interpretation of the response in terms of known phenomena and processes. In practice, exposure-assessment models will probably contain both mechanistic and empirical elements.

Estimates of exposure can also be viewed from a temporal perspective: they can be defined as static or dynamic. Static estimates relate to a particular point in time, e.g. the probability and level of exposure associated with a random serving of the food product, or the number of contaminated servings consumed per year. In contrast, a dynamic approach would consider the way in which exposure changes over time, for example, reflecting seasonality of exposure (Anderson and May, 1992; Bailey, 1975) or the increasing contamination of a processing line as time from last clean-up increases (Nauta, Van der Fels-Klerx and Havelaar, 2005; Zwietering and Hasting, 1997a, 1997b).

12. Predictive Microbiology

Predictive microbiology can play an important role in exposure assessment and is used to fill in data gaps that would otherwise require more extensive data collection programmes. Predictive microbiology, in conjunction with mathematical models describing various environmental factors, e.g. including storage time and temperature, pH, water activity, etc., can be used to estimate the final level/concentration of pathogens or spoilage organisms in the food. For example, while the number of pathogenic bacteria in food at retail may be available, the number in the food immediately prior to consumption is not. It may, however, be possible to model the number of pathogenic bacteria in the food immediately prior to consumption, considering the storage, preparation and cooking conditions.

Predictive microbiology also has limitations. Not all hazards that are of interest have been characterized – and therefore not all microbial kinetic parameters are available, uncertainties surrounding predictions are not always given, and predicted values may not truly represent the real world if models have not been validated. In spite of the limitations, predictive models remain valuable tools for exposure assessment of pathogenic microorganisms in foods. Detailed descriptions of the application of predictive microbiology in MRA can be found in Ross and McMeekin (2003) and Ross (2008).

12.1 Modelling microbial growth and inactivation

12.1.1 *Microbial ecology of foods*

The possible responses of most microorganisms in foods include stasis, growth or death. In general, viruses and protozoa ('parasites') are inert in foods, requiring a living 'host' to be able to reproduce. While they cannot grow, they can be inactivated by various treatments and processing steps. Similarly, prions are not infectious organisms but are proteins. While they also cannot grow in foods they may be inactivated by some treatments, although they are very resistant to denaturation.

Populations of microorganisms in foods may display stasis, growth or death, depending on the formulation of the food ('intrinsic' factors) and the processing, distribution or storage conditions ('extrinsic' factors). They may even display different responses at different times in a single unit of food because conditions can change during processing, transport, storage and preparation.

While each organism may have a qualitatively similar response to changes in temperature, pH, preservatives, etc., the magnitude and type of response (e.g. growth, death, stasis) to different levels of these factors is specific to the hazard in question. While pH, water activity and temperature are the most frequently cited properties and typically have the greatest effect on microbial behaviour, many foods will have additional properties with important consequences. These include the levels of fat, oxygen, phosphates, certain spices, organic acid anions (especially acetate, lactate, sorbate and benzoate), nitrite, ionic and non-ionic humectants (sugars, salts, etc.), and antimicrobials such as benzoate or sorbates. Food structure has also been shown to play an important role in influencing microbial behaviour in some foods (e.g. Wilson *et al.*, 2002).

To estimate exposure at the time of consumption, it will be necessary to model the cumulative effect over time of the food's composition (which may change over time) and processing or storage conditions on the microbiological hazard. In some cases, changes in microbial numbers during processing may occur as a result of cross-contamination, rather than growth or inactivation. Note that the same considerations may apply to microorganisms in water, whether recreational or for drinking and food preparation or irrigation.

It is important to understand under what circumstances growth, inactivation or cross-contamination may need to be considered. In Table 39 are provided indicative values, based on expert opinion, for the effect of temperature on the rates of growth or inactivation of many vegetative bacteria; inactivation of endospores requires considerably longer time and/or higher temperature. Growth rates for fungi will be slower, but inactivation rates are generally in the same range.

Table 39: Indicative response times for growth and inactivation of vegetative bacterial cells as a function of temperature.

Temperature (°C)	Time for 10-fold increase in numbers (hours)	Time for 10-fold *decrease* in numbers (for vegetative cells)
-80		years to decades
-20		months
0	15-75	
5	10-30	
10	5-20	
20	3-10	
30	2-3	
35	1-2	
50	growth not possible for most	days to weeks
60		hours
70		seconds to minutes
80		fractions of seconds to seconds

Each type of microorganism has a finite range of temperatures over which it can grow, some preferring lower temperatures, others higher temperatures. Note also that the effect of temperature depends on the temperature range considered. At low temperature, survival is enhanced, while at intermediate temperatures, growth rate increases with increased temperature. At temperatures above the limit for growth, however, death results at a rapidly increasing rate with increasing temperature.

Each organism also has a finite range for growth as a function of pH, water activity, organic acid level, preservatives, etc., so that there are upper and lower limits for each factor, as well as an optimal level at which the growth rate is fastest. In general, the inhibitory effects of suboptimal factors interact both to reduce the range of each factor over which growth is possible when one or more factors are suboptimal, and to reduce the overall growth rate. At conditions beyond those that allow growth, stasis – or more probably death – will result at a rate dependent on the conditions but that is apparently most strongly influenced by the temperature (McQuestin, Shadbolt and Ross, 2009; Zhang *et al.*, 2010).

The growth of microorganisms in a unit of food follows the pattern of a 'batch' culture, often with a period of adjustment ('lag'), involving no growth, followed by exponential growth until some maximum population density (MPD) is reached and population growth ceases (see Figure 13). For many organisms and many foods, the MPD is in the range 10^9-10^{10} cells per gram, ml or cm^2 of food.

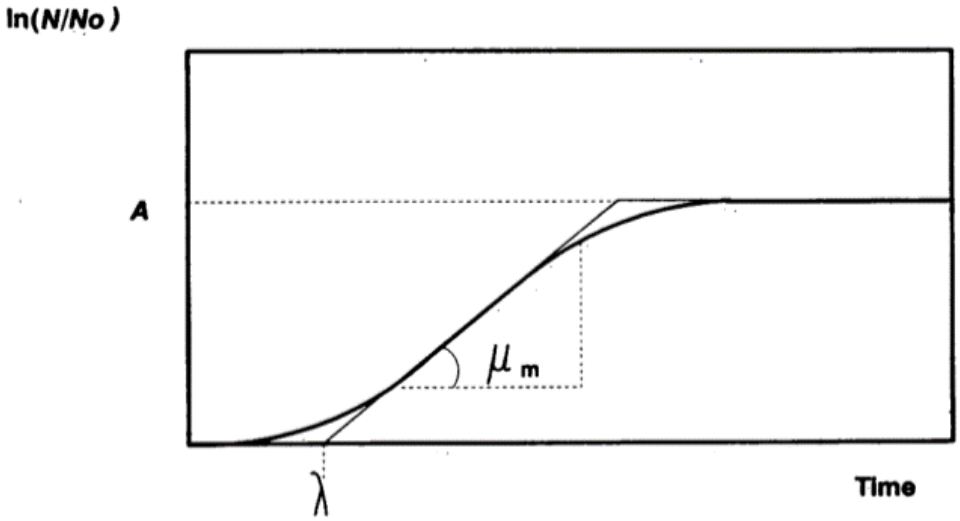

Figure 13: Example of a typical growth curve where A denotes the maximum population density, λ denotes the lag and μ_m denotes the maximum growth rate (Fig 1 of Zwietering et al., 1990)

Similarly, the death or inactivation of microorganisms in a unit of food is characterised by an initial period of no decrease in the microbial population ('shoulder'), followed by an exponential death phase until the 'tail' is reached and population decline ceases.

Although the ecology of microbiological hazards in food can be complex, predictive microbiology models can be used to estimate changes in microbial levels in foods as the product moves through the farm-to-fork chain. Ross (2008) provides a detailed discussion of the microbial ecology of foods in the context of the exposure assessment part of risk assessment.

12.1.2 *Predictive microbiology*

In recent years, significant advances have been made in the field of predictive microbiology. Some models are based on data obtained from liquid microbiological media and have been developed to predict the microbial behaviour when the physicochemical characteristics of the food (e.g. pH, water activity, organic acids concentrations) and the storage temperature are known. Some of these models can fail to accurately describe the microbial behaviour in foods, although the more robust models of this type have been validated in foods. Some other models have been developed to predict the behaviour of micro-organisms in particular foods whatever their storage conditions might be. The food-based models can effectively describe the impact of storage conditions on a specific food but their ability to describe the impact of the variability of physicochemical characteristics of the food or to make predictions in other foods is questionable. Some intermediate approaches have also been developed trying to overcome the limitations of these two major approaches. For certain products, it has been shown that proliferation (rate or extent, or both) of the spoilage microflora of a product influences the behaviour of the pathogen concerned, e.g. *L. monocytogenes* on cheese and cold-smoked salmon (Giménez and Dalgaard, 2004; Mellefont, McMeekin and Ross, 2008; Cadavez *et al.*, 2019).

For many bacterial pathogens, responses to environmental conditions have been described and summarized in mathematical models that can be used to predict their behaviour in foods, including growth rate, lag time, death rate, probability of growth occurring, and probability of toxin production within the storage life of the product. Models relating the number of a microbial organism and time, assuming that all other factors are constant, are known as primary models (Buchanan, 1993).

The physiological and physical state of the microorganism in the food remains a relatively unexplored area. Stress, injury and recovery also affect the initiation of growth. Spores will have a distribution of germination/outgrowth/lag times. Many studies use stationary phase cells grown in a nutrient-rich broth at favourable temperatures, and the predicted lag phase duration represents those conditions; cells that contaminate a food may be in a different physiological state. The extent to which the organism is clustered or aggregated may influence growth, survival and cross-contamination.

In predictive microbiology, foods are characterized in terms of their properties that most affect microbial growth and survival, such as temperature, pH, organic acid levels, salt levels and preservative levels. Microbial responses to analogous conditions are systematically studied and quantified, usually in a simplified laboratory broth model system under static and axenic conditions. The data are collated and summarized as predictive mathematical models. In particular, models that relate these properties to growth rate are known as secondary models (Buchanan, 1993).

Tertiary models are usually considered models that combine primary and secondary models (Buchanan, 1993). However, it has been argued that the term 'tertiary models' "should be used for patterns in the parameters of the secondary models as a function of the organism and the nutrient source" (Baranyi, Buss da Silva and Ellouze, 2017).

Conditions actually experienced by the foods and microbes are dynamic, and the effects of those conditions on rates of growth or inactivation have to be mathematically integrated over time for each of those distinct processes or stages. Thus, measurements of processing and handling parameters, and the duration for which these conditions are experienced, are integrated and used to predict changes in hazard levels (i.e. population size or concentration) in the food or water. Some predictive microbiology models, however, recreate the growth curve, i.e. the number of cells present, assuming a defined starting level, as a function of incubation time. Outputs from such models would normally have to be converted to rates of growth before their application in exposure assessment models.

A potential weakness of many predictive models is that they are developed in laboratory broth media, in which factors such as interactions with other microbes in the food or effects due to the physical structure of some foods are not observed. In general, these limitations relate to a few specific types of products, e.g. lactic acid bacteria may suppress pathogen growth in vacuum-packed or modified-atmosphere packed foods, matrix effects may be important in water in oil emulsions (e.g. butter). While most models have been developed in laboratory broth, models for some microorganisms have been developed in specific foods of concern or interest.

12.1.3 *Model types and modelling tools*

Models are available that describe:

- Rates of growth as a function of multiple environmental factors.
- Rates of inactivation, most as a function of a single lethal factor. One should be aware, however, that microbial inactivation is usually considered a stochastic process, i.e. the probability of survival of cells decreases (more or less) exponentially per unit of time. Thus, although the number of viable cells in an individual unit of food may be predicted to be less than one, one might still find survivors if a larger unit of the product (e.g. the total volume of a batch), or many units of the product, were examined or considered.

- Limits to growth as a function of multiple environmental factors, so-called 'growth/no growth' or 'interface models'. Absolute limits to growth of many pathogens due to individual environmental variables have been documented (ICMSF, 1996).
- Probability of growth or toxigenesis within a defined period as a function of multiple environmental factors.

In addition to numerous small-scale research projects to model microbial responses in foods, two large-scale predictive microbiology research programmes were undertaken in the early 1990s. They were funded by the governments of the United States of America and of the United Kingdom and resulted in the development of a suite of models for responses of populations of foodborne microbial pathogens and some spoilage organisms. The outcomes of those programmes, and subsequent developments, are now available without cost through the Predictive Microbiology Information Portal[17] which hosts the Pathogen Modelling Program and links to ComBase and ComBase Predictor[18]. These software packages include growth models for many pathogens and some spoilage organisms, and inactivation models for some pathogens. ComBase is a database of observations for many published and unpublished sources on microbial growth and inactivation rates, and at the time of writing contains approximately 60,000 records. The database is derived from the USA and UK government-funded research programmes referred to above, from data extracted from the published literature and from data (both published and unpublished) donated by researchers and research organizations around the world. Additional models for a range of pathogens and spoilage organisms are also available (Microsoft Windows only) from the Danish Technical University – Food Spoilage and Safety Predictor Web site[19]. Comprehensive lists of predictive microbiology modelling tools are available on the Combase[20] and the OpenML for Predictive Modelling in Food[21] websites, as well as Koutsamanis *et al.* (2016). The available tools offer a variety of utilities for the majority of foodborne pathogens including databases, fitting tools, predictions for growth, growth/no growth and inactivation, probabilistic models, and risk assessment modules. This allows for a wide range of applications including exposure assessment. The most important benefit for the users, however, is that software can assist decision-making in a short-time frame and allow practices to be actioned almost in real time.

Additionally, there are many modelling programmes and studies that have not resulted in the release of software but that are published (often including the data on which the model is based) in the scientific literature. These can be found readily by undertaking a literature search.

The integration of models for microbial growth, growth limits or inactivation into unified models that can predict both increases and decreases in microbial populations over time will also improve the utility of predictive models for exposure assessment. Several unified models have been proposed, but none have been widely used or endorsed.

Many reviews of predictive microbiology, including potential pitfalls, have been published. McMeekin *et al.* (1993) and Ross *et al.* (2014) provide a good introduction to the concept and its practical application, and the texts edited by McKellar and Lu (2003), Brul *et al.* (2007) and Pérez-Rodríguez and Valero (2013) provide more contemporary reviews of the state of the art. An

[17] https://portal.errc.ars.usda.gov/ accessed 20 June 2019
[18] http://www.combase.cc accessed 20 June 2019
[19] http://fssp.food.dtu.dk/ accessed 20 June 2019
[20] https://www.combase.cc/index.php/en/8-category-en-gb/21-tools accessed 29 November 2018
[21] https://sourceforge.net/p/microbialmodelingexchange/wiki/Tools/ accessed 29 November 2018

extensive listing of available predictive microbiology models was presented in Ross and Dalgaard (2004).

12.2 Application of predictive microbiology within exposure assessment

In practice, two features of a predictive microbiology model are critical to its utility. One is the ability to predict accurately microbial responses under all conditions to which the model applies. Evaluation of this ability is loosely termed 'model validation' (see Section 16.2.3). The second is the range of independent variables and variable combinations to which the model applies – if the model does not include terms for all factors of relevance to the microbial ecology of the hazard in the food, then that model is 'incomplete.' While predictive microbiology has matured considerably as a science discipline over the last two decades many currently available models are still incomplete or unvalidated, or both. Thus, exposure modelling should include consideration of the validity and reliability of predictive microbiology models, if used.

12.2.1 *Range of model applicability*

No predictive models currently in use are fully mechanistic (i.e. derived entirely from fundamental theoretical bases), therefore microbial growth or death cannot be reliably predicted in a food in which the conditions are beyond the range of any individual factor included in the data used to develop the model (i.e. predictions should be made by interpolation only).

Different models have different interpolation regions depending on the experimental design used to develop the model. The determination of the true interpolation region and the consequences of extrapolation were discussed by Baranyi *et al.* (1996). Those authors concluded that models that were over-fitted using a large number of parameters were more prone to unreliability resulting from inadvertent extrapolation, because the predictions of the model often changed dramatically near the limits of the interpolation region.

Inadvertent extrapolation can also occur when using stochastic modelling techniques to describe effects of fluctuating variables. This problem may occur for any factor, but temperature is the factor most likely to fluctuate in most real-world examples. Consideration should be given to truncating the tails of the temperature (and other) distributions used to predict microbial growth or death, if necessary, to match the interpolation range of the predictive microbiology model used. This should be done by utilizing a suitable 'truncated' distribution so that the mean, variance and other properties of the chosen distribution are not changed in unintended ways (Johnson, A. W. Kemp and Kotz, 2008). The growth limits for the pathogen of concern, and potential for inactivation (if conditions are beyond those limits) should be considered and included in exposure modelling. Growth/no growth models may assist in this regard and have been included in some exposure assessment models.

12.2.2 *Spoilage microbiota*

The effect of spoilage bacteria on the shelf life of the product should also be considered. Conditions that lead to rapid growth of pathogens may also lead to rapid microbial spoilage. Contaminated products that are obviously spoiled are less likely to be consumed, and thus do not lead to foodborne disease, despite that fact that they contain a microbiological hazard. Thus, it may be necessary to consider the effect of storage conditions on the shelf life of the product in case unrealistically long times at high temperatures are simulated. This can be implemented by correlating model variables that affect growth (e.g. storage time and temperature). Stochastic modelling texts offer advice on how such correlations can be included in models and examples include Ross *et al.* (2009), Smith *et al.* (2013) and Kiermeier *et al.* (2015).

On a related topic, other microorganisms growing in the food can influence the potential growth of pathogens. Exposure assessments that rely on empirical data derived from pure culture broth systems are likely to overestimate potential growth of pathogens in food matrices due to the co-existence of numerous competing bacterial population (Coleman, Sandberg and Anderson, 2003). Pathogen growth rates and maximum densities are thought to be a function of the total microbial community composition and density in the food due to competition for nutrients, the production of inhibitory substances, and overall density (Powell, Schlosser and Ebel, 2004). The final cell density of a pathogenic bacterium can be suppressed when the total concentration of all bacteria in the food reaches stationary phase, a phenomenon that has been termed the 'Jameson Effect' (Jameson, 1962; Stephens *et al.*, 1997) and reported by many authors (e.g. Ross, Dalgaard and Tienungoon, 2000; Le Marc, Valík and Medveďová, 2009; Al-Zeyara, Jarvis and Mackey, 2011). In many foods, this effect will not happen before spoilage occurs, but in vacuum-packed or modified-atmosphere packed foods such as processed meats and lightly preserved fish, lactic acid bacteria can reach stationary phase without causing overt spoilage and limit the growth of pathogens to safe levels within the acceptable shelf life of the product.

12.2.3 *Sources of variability and uncertainty*

In stochastic modelling, it is important to characterize the magnitude of the variability and its distribution about the mean. Traditionally, the approach to fit predictive microbiological models was through a 2-step fitting approach. For example, first primary models were fitted separately for each temperature and the model parameter estimates were extracted (esp. max growth rate). Subsequently these estimates were used as the response for the secondary model, i.e. the model was fitted to relate them to temperature; the implicit assumption is that the parameter estimates are known values rather than estimates. This approach was likely due to the nonlinear nature of problem (i.e. when primary and secondary models are combined) and the result of limited computing power in the early days of the discipline. However, fitting nonlinear models is no longer a major problem, though the actual fitting process can still be problematic; good starting estimates and suitable parameter transformations can help in this regard. In addition, it has been shown that the 1-step model fitting process, i.e. where the primary and secondary models are combined and estimated in a single model, is more efficient, and hence to be preferred, than the 2-step process (Jewell, 2012; Dolan and Mishra, 2013; Huang, 2017).

Distribution of response times

Using the limited amount of replicated published data concerning growth rate estimates under varying environmental conditions, Ratkowsky *et al.* (1991) concluded that growth rates became increasingly variable at slower growth rates. Microbial response times or rates as a function of environmental conditions are often not normally distributed. Distributions describing growth rate and/or response time variability in response to temperature have been described by various researchers (Ratkowsky *et al.*, 1991, 1996; Alber and Schaffner, 1992; Dalgaard *et al.*, 1994; Zwietering *et al.*, 1994). Ratkowsky (1992) presented a general relationship between the variance in growth response times and the mean of those responses for a range of possible distribution types.

Sources and magnitude of errors

Model predictions can never perfectly match observations or represent reality. Each step in the model construction process introduces some error as described below (Cullen and Frey, 1999; Ross, McMeekin and Baranyi, 2014).

- *Homogeneity* error arises because some foods are clearly not homogeneous. Current predictive models do not account for this non-homogeneity of foods.

- *Completeness* error in predictive models arises because the model is a simplification, and other food effects and microbial ecology effects (structure, competition, etc.) that are difficult to quantify are not included in currently available models.
- *Model function* error is similar to completeness error and arises mainly from the compromise made when using empirical models, namely that the model is only an approximation to reality.
- *Measurement* error originates from inaccuracy in the limitations in the measurement methods used to collect raw data that are used to estimate the parameters of a model.
- *Numerical procedure* error includes all errors arising from procedures used for model fitting and evaluation, some of which are only methods of approximation.

Like all statistical models, the fit of the model should be checked graphically against the actual observations. Sometimes the fitted model clearly doesn't match the data very well, in which case a different model formulation may need to be considered.

As rule of thumb, when constructing a predictive microbiology model from data, each additional variable increases the error in the estimate of the specific growth rate by approximately 10% (Ross, McMeekin and Baranyi, 2014). In other words, confidence in the predicted growth rate, and total predicted growth declines when more variables that affect the growth rate are considered. The significance of this for predicted exposure depends on the amount of growth predicted to occur. For a three-factor/variable model the magnitude of the 'error' in terms of growth rate and log number of cells would be around ±30%, irrespective of the amount of growth predicted. However, in many situations, probability of infection (and thus risk) is related to the absolute number of cells ingested, not the logarithm of dose. Thus, if one generation of growth ($0.30\ \log_{10}$) were predicted (assuming the lag time and maximum population density are known exactly and not estimated), the error in the predicted number of cells would be $\pm(0.30\ \log_{10} \times 0.3)$, i.e. ±23% of the estimate. If 10 generations of growth were predicted, the 'error' would be $\pm(3.00\ \log_{10} \times 0.3)$ which, in terms of numbers of cells would be ±800%. If lag time and MPD are also estimated, then these errors will be larger.

13. Dose-Response

The assumptions on which current models are based, their use and possible limitations are carefully considered in the following sections.

Dose-response modelling requires a combination of mathematics, statistics, human biology (infection process, immune system), microbiology and epidemiology. Different approaches are available for model fitting and the assumptions underlying the dose-response model need to be understood, assessed and reported/communicated.

The focus of these sections is on infectious and toxico-infectious hazards, as this has been the area of most development. However, it should be noted that this chapter provides an overview of dose-response models and the interested reader is directed to the review by Haas (2015), which provides information on D-R models not only for foodborne hazards.

13.1 The infectious disease processes

The biological basis for dose-response models derives from major steps in the disease process as they result from the interactions between the hazard, the host and the matrix. Figure 14 illustrates the major steps in the overall process, with each step being composed of many biological events. Colonization, toxin production, infection and illness can be seen as resulting from the hazard successfully passing multiple barriers in the host. These barriers are not all equally effective in eliminating or inactivating hazards and may have a range of effects, depending on the hazard and the individual. Each individual hazard has some particular probability to overcome a barrier, which is conditional on the previous step(s) being completed successfully, similar to the *hurdle concept* in food processing. The disease process as a whole, and each of the component steps, may vary by hazard and by host. Hazards and hosts can be grouped with regard to one or more components, but this should be done cautiously and transparently.

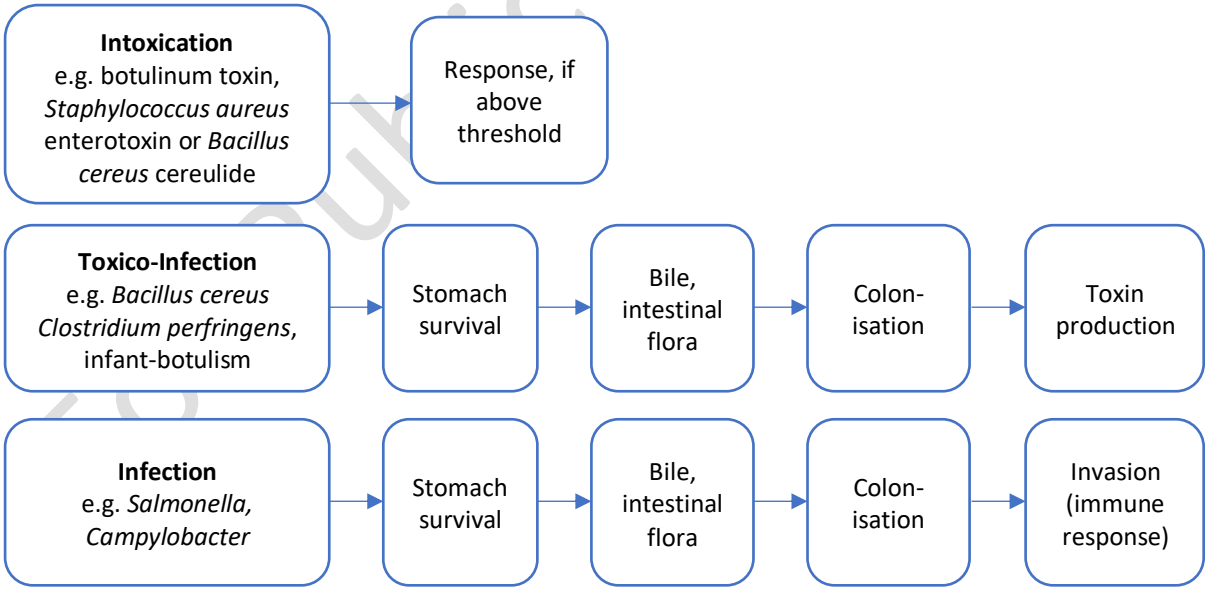

Figure 14: The major steps in the foodborne infectious disease process.

13.1.1 *Infection*

Infection is usually measured as a quantal response, i.e. the presence or absence of infection by some criterion. The use of continuous-response variables, e.g. an antibody titre, may be useful for further development of dose-response models.

There are usually many different and simultaneous signs and symptoms of illness in any individual, and the severity of symptoms varies among hazards, strains and among hosts infected with the same hazard. The extent of illness is therefore a process that can also be measured on a multidimensional, quantitative, continuous scale (number of stools passed per day, body temperature, laboratory measurements, etc.).

A wide variety of case definitions for gastrointestinal illness are used in the literature, based on a variable list of symptoms, with or without a specified time window, and sometimes including laboratory confirmation of etiological agents. This lack of standardization severely hampers integration of data from different sources.

13.1.2 *Sequelae and mortality*

In a small fraction of ill persons, chronic infection or sequelae may occur. Some pathogens, such as *Salmonella enterica* serotype Typhi, are invasive and may cause bacteraemia and systemic infections. Other pathogens produce toxins that may result not only in enteric disease but also in severe damage in susceptible organs. An example is haemolytic uraemic syndrome, caused by damage to the kidneys from Shiga-like toxins of some *Escherichia coli* strains. Complications may also arise by immune-mediated reactions: the immune response to the pathogen is then also directed against the host tissues. Reactive arthritis, including Reiter's syndrome, and Guillain-Barré syndrome are well known examples of such sequelae. The complications from gastroenteritis normally require medical care, and frequently result in hospitalization. There may also be a risk of mortality in relation to sequelae, and not all patients may recover fully, but may suffer from residual symptoms, which may last a lifetime. Therefore, despite the low probability of complications, the public health burden may be significant. Also, there is a direct risk of mortality related to acute disease, in particular in the elderly, neonates and severely immunocompromised.

In the context of a risk assessment, the number of cases with sequelae and complications are usually ascertained on a proportional basis, similar to the approach used by the WHO Foodborne Disease Burden Epidemiology Reference Group (Section 4.2, WHO, 2015).

13.2 Modelling concepts

13.2.1 *The particulate nature of the inoculum.*

It is commonly assumed that the organisms are randomly distributed in the inoculum, but this is rarely the case. The Poisson distribution is generally used to characterize the variability of the individual doses when pathogens are randomly distributed.

Compound distribution or over-dispersion may result from two different mechanisms:

a) A "unit" as detected by the measurement process (e.g. a colony-forming unit (CFU), a tissue culture infectious dose, or a Polymerase Chain Reaction (PCR) detectable unit) may, due to aggregation, consist of more than one particle. This is commonly observed for viruses (e.g. Teunis *et al.*, 2008), but may also be the case for other pathogens (e.g. Jongenburger *et al.*, 2011). The degree of aggregation strongly depends on the methods used for preparing the inoculum. It is important to know whether the aggregates remain intact during inoculum preparation or in the gastrointestinal tract.
b) In a well-homogenized liquid suspension, single disaggregated organisms will be more or less randomly distributed. If the inoculum consists of a solid or semisolid food matrix, however, spatial clustering may occur and result in over-dispersion of the inoculum (e.g. Jongenburger *et al.*, 2012). This aspect of spatial clustering may differ between the data underlying the dose-response model and the actual exposure scenario.

The reason why knowing about aggregation is important is that it can have an effect on the dose-response model and thus the estimated 50% infectious dose ID_{50}. For example, for norovirus it was found that the ID_{50} was 1,015 genome copies for the aggregated inoculum, while for the disaggregated virus the ID_{50} was only 18 viruses (Teunis et al., 2008) – approximately two orders of magnitude lower!

13.3 Selection of models

Specific properties in the data become meaningful only within the context of a model. Different models may, however, lead to different interpretations of the same data, and so a rational basis for model selection is needed. Different criteria may be applied when selecting mathematical models. For any model to be acceptable, it should satisfy the statistical criteria for goodness of fit, in particular, residual plots are essential tools for assessing goodness of fit. In the case of more than one model fitting equally well, goodness of fit statistics, such as the various likelihood-based Information Criteria, can be used to select "the best" (Dziak *et al.*, 2018). However, many different models will usually fit a given data set (e.g. Holcomb *et al.*, 1999) especially due to the large variability and uncertainty in the data and therefore goodness of fit is not a sufficient criterion for model selection. Additional criteria that might be used are conservativeness, flexibility, parsimony and biological plausibility.

A conservative model is one that tends to over-predict the response of interest (i.e. in the context of a D-R model this is the probability of infection or illness). However, conservativeness can be approached in different ways: "Is the model structure conservative?", "Are parameter estimates conservative?", "Are specific properties, e.g. prediction at low doses, of the model conservative?" and so forth. It is not recommended to build conservativeness into the model structure itself.

From a risk assessment perspective, a model should be restricted to describing the data and trying to discriminate the biological signal from the noise. Adding parameters usually improves the goodness of fit of a model but using a flexible model with many parameters may result in overfitting (Lever, Krzywinski and Altman, 2016; Steyerberg *et al.*, 2010) – a lack of parsimony – and greater uncertainty of estimates, especially for extrapolated doses.

It is recommended that dose-response models be biologically plausible. For example, a quadratic model may fit a given data set well, or even better than an alternative model, yet the quadratic model is not biologically plausible and will result in inappropriate predictions when extrapolated to very small or large doses. Note that it is generally not possible to "work back", i.e. to deduce the assumptions underlying a given model formula. There is a problem of identifiability: the same functional form may result from different assumptions, while two (or more) different functional forms (based on different assumptions) may describe the same dose-response data equally well. This can result either in very different fitted curves if the data contain little information, or virtually the same curves if the data contain strong information. However, even in the latter case, the model extrapolation may be very different. This means that a choice between different models or assumptions cannot be made on the basis of data alone (e.g. FAO/WHO, 2011b, Annex A1.1.1).

13.3.1 *Dose-infection models*

Consider a host who ingests exactly one cell of a pathogenic microorganism. According to the single-hit hypothesis, the probability that this pathogen will survive all barriers and colonize the host has a non-zero value of p. Thus, the probability of the host not being infected is $1-p$. If a second cell of the pathogen is ingested, and the hypothesis of independent action is valid, then the probability of the host not being infected is $(1-p)^2$. For n pathogens, the probability of not being infected is $(1-p)^n$. Hence, the probability of infection of a host that ingests exactly n pathogens can be expressed as:

$$P_{inf}(n \mid p) = 1 - (1 - p)^n$$

When the discrete nature of pathogens is also taken into account, these concepts lead to the single-hit family of models.

13.3.2 *Dose-illness models*

The default assumption of constant probability models for illness given infection leads to the conclusion that the only difference between dose-infection and dose-illness models is that the dose-illness models do not need to reach an asymptote of 1 because the probability of illness given infection can be something less than one when the probability of illness given dose approaches 1 (Teunis and Havelaar, 2000; Teunis, Nagelkerke and Haas, 1999). As such they essentially still belong to the family of hit-theory models.

13.3.3 *Sequelae and mortality*

Given illness, the probability of sequelae or mortality, or both, depends on the characteristics of the pathogen, but more importantly on the characteristics of the host. Sequelae or mortality are usually rare events that affect specific subpopulations. These may be identified by factors such as age or immune status, but increasingly genetic factors are being recognized as important determinants. As for dose-illness models , the current possibilities are mainly restricted to constant probability models (e.g. FSIS, 2001). In the case of mortality, the proportion of infected patients who died is known as the *mortality ratio*. Stratification appears to be necessary in almost all cases where an acceptable description of risk grouping is available.

13.4 Extrapolation

13.4.1 *Low dose extrapolation*

Dose-response information is usually obtained in the range where the probability of observable effects is relatively high. In experimental studies using human or animal subjects, this is related to financial, ethical and logistical restrictions on group size. In observational studies, such as outbreak studies, low dose effects can potentially be observed directly, but in these studies only major effects can be distinguished from background variation. The single-hit family of models (further exemplified in Section 13.5) is characterized by linear low dose extrapolations on the log/log scale, or even on the arithmetic scale. That is, in the low dose range, the probability of infection or illness increases linearly with the dose and hence on the log-scale, these models have a slope of 1 at low doses (see for example Figure 8). Some model examples include:

• The Binomial model	$P_{inf}(n \mid p_1) = 1 - (1 - p_1)^n$	$P_1 = p_1$
• The linear model	$P = r \times D$	$P_1 = r$
• The exponential model	$P = 1\text{-}\exp(-r \times D)$	$P_1 = 1\text{-}\exp(-r) \approx r$
• Beta-Poisson model	$P = 1\text{-}[1+D/\beta]^{-\alpha}$	$P_1 \approx (\alpha/\beta)$
• The hypergeometric model	$P = 1\text{-}{}_1F_1(\alpha, \alpha+\beta, -D)$	$P_1 \approx \{\alpha/(\alpha+\beta)\}$

where D = mean ingested dose and r, α and β are model parameters. Note that if $\alpha > \beta$, the probability of infection predicted by the Beta-Poisson model is larger than one, which is not biologically plausible.

13.4.2 *Extrapolation in the pathogen-host-matrix triangle*

Experimental datasets are usually obtained under carefully controlled conditions (e.g. using specific strains), and the data apply to a specific combination of pathogen, host and matrix. In actual exposure situations, there is more variability in each of these factors, and dose-response models need to be generalized. Assessing such variability requires the use of multiple datasets that capture

5219 the diversity of human populations, pathogen strains and matrices. Failure to take such variation
5220 into account may lead to underestimation or overestimation of the actual risk of the outcome of
5221 interest.

5222 When developing dose-response models from multiple datasets, one should use all the pertinent
5223 data. This requires that the risk assessors make choices about how to use different datasets. Such
5224 choices should be based on objective scientific arguments but will inevitably include subjective
5225 arguments. Such arguments should be fully and transparently documented and ideally be discussed
5226 with the risk manager and their significance and impact for risk management considered. The
5227 credibility of dose-response models increases significantly if dose-response relations derived from
5228 different data sources are consistent.

5229 When combining data from different sources, a common scale on both axes is needed. This often
5230 requires adjusting the reported data to make them comparable. For the dose, test accuracy, sample
5231 size, etc., need to be taken into account. For the response, a consistent case definition is needed, or
5232 the reported response needs to be adjusted to a common denominator (e.g. infection × conditional
5233 probability of illness given infection). Combining data from different sources within a single
5234 (multilevel) dose-response model requires thorough statistical skills and detailed insight into the
5235 biological processes that generated the data. An example is the multilevel dose-response model that
5236 has been developed for different isolates of *Cryptosporidium parvum* (Teunis, Chappell and
5237 Okhuysen, 2002a). The issue of combining data from different outbreak studies is discussed in the
5238 FAO/WHO risk assessments of *Salmonella* in eggs and broiler chickens (FAO/WHO, 2002a).

5239 Dose-response relations where the hazard only affects a portion of the population do require that
5240 subpopulations be separated from the general population to generate meaningful results. Using
5241 such stratified dose-response models in actual risk assessment studies requires that the percentage
5242 of the population that is actually susceptible can be estimated. Consideration of such subpopulations
5243 appears to be particularly important when attempting to develop dose-response relations for
5244 serious infections or mortality. However, it would also be pertinent when considering a hazard for
5245 which only a portion of the population can become infected, e.g. not all people are susceptible to
5246 norovirus infection (Teunis *et al.*, 2008).

5247 A particular and highly relevant aspect of microbial dose-response models is the development of
5248 specific immunity in the host. Most volunteer experiments have been conducted with test subjects
5249 selected for absence of any previous contact with the pathogen, usually demonstrated by absence of
5250 specific antibodies. The actual population exposed to foodborne and waterborne pathogens will
5251 usually be a mixture of totally naive persons and persons with varying degrees of protective
5252 immunity. No general statements can be made on the impact of these factors. This is strongly
5253 dependent on the pathogen and the host population. Some pathogens, such as many childhood
5254 diseases and the hepatitis A virus, will confer lifelong immunity upon first infection whether clinical
5255 or subclinical, whereas immunity to other pathogens may wane within a few months to a few years,
5256 or may be evaded by antigenic drift. At the same time, exposure to non-pathogenic strains may also
5257 protect against virulent variants. This principle is the basis for vaccination, but has also been
5258 demonstrated for natural exposure, e.g. to non-pathogenic strains of *Listeria monocytogenes*
5259 (Notermans *et al.*, 1998). The degree to which the population is protected by immunity depends to a
5260 large extent on the general hygienic situation. In many developing countries, large parts of the
5261 population have built up high levels of immunity, and this is thought to be responsible for lower
5262 incidence or less serious forms of illness. Some examples are the predominantly watery form of
5263 diarrhoea by *Campylobacter* spp. infections in children and the lack of illness from this organism in
5264 young adults in developing countries. The apparent lack of *E. coli* O157:H7-related illness in Mexico

has been explained as the result of cross-immunity following infections with other *E. coli*, such as enteropathogenic *E. coli* strains that are common there. Obviously, age is an important factor in this respect, as older people will have greater likelihood of prior exposure than children. In contrast, in the industrialized world, contact with enteropathogens is less frequent and a larger part of the population is susceptible. This also highlights that dose-response models may not be globally applicable.

Incorporating the effect of immunity in dose-response models has received little attention. The absence of accounting for immunity in dose-response models may complicate interpretations, and comparisons among geographic regions. This is particularly likely to be a problem with common infections such as *Campylobacter* spp., *Salmonella* spp. and pathogenic *E. coli*. Immunity may affect the probability of infection, the probability of illness given infection, or the severity of illness. There are currently only few data sets available on which to base model development. Where such data are available, a simple and possibly effective option would be to resort to stratified analysis and divide the population into groups with different susceptibility (e.g. FDA/FSIS, 2003; Pouillot *et al.*, 2015b; Teunis *et al.*, 2008). Experimental work on infection of volunteers having different levels of acquired immunity to *Cryptosporidium parvum* was analysed with a dose-response model that includes the effects of immunity (Messner and Berger, 2016; Teunis, Chappell and Okhuysen, 2002b).

Stratified analysis can also be useful when dealing with seemingly outlying results, which may actually indicate a subpopulation with a different response. Removal of one or more outliers corresponds to removing (or separately analysing) the complete group from which the outlying results originated. Where a specific reason for the separation cannot be identified, there should be a bias toward being inclusive in relation to the data considered. As for all data analysis, any exclusion of the outlying data should be scientifically justified and clearly communicated to ensure the transparency of the assessment.

13.5 Dose-response model fitting approaches

According to the single-hit hypothesis (see Section 6.3 and 13.3.1), the probability of infection of a host that ingests exactly *n* pathogens can be expressed as:

$$P_{inf}(n \mid p) = 1 - (1 - p)^n$$

This model is also called the *binomial dose-response model*. Starting from this basic function and taking the discrete nature of pathogens into account, a broad family of dose-response models (hit-theory models) can be derived. The most frequently used models are the exponential and the Beta-Poisson models, which are based on further assumptions on the distribution of pathogens in the inoculum, and on the value of p. When the distribution of the organisms in the inoculum is assumed to be random, and characterized by a Poisson distribution, it can be shown (Teunis and Havelaar, 2000) that the probability of infection as a function of the dose is given by:

$$P_{inf}(D \mid p) = 1 - \exp\{-Dp\}$$

where D is the *mean* ingested dose (while the *n* above is the *exact* number of organisms ingested). This model gives virtually the same outcome as the above binomial model. If p is assumed to have a constant value *r* for any given host and any given pathogen, the simple exponential model results:

$$P_{inf}(D \mid r) = 1 - \exp\{-rD\}$$

When the dose is low and $rD << 1$, then this formula is approximated by a straight line, i.e.

$$P_{inf}(D \mid r) \approx rD$$

If the probability of starting an infection differs for any organism in any host, and is assumed to follow a beta-distribution, then:

$$P_{inf}(D \mid \alpha, \beta) = 1 - {}_1F_1(\alpha, \alpha+\beta, -D)$$

Where ${}_1F_1()$ is the Kummer confluent hypergeometric function (Abramowitz and Stegun, 1972), which can also be found in the Digital Library of Mathematical Functions (https://dlmf.nist.gov/). For $\alpha << \beta$ and $\beta >> 1$, P_{inf} is approximately equal to the Beta-Poisson formula:

$$P_{inf}(D \mid \alpha, \beta) \approx 1 - (1 + D/\beta)^{-\alpha}$$

As for the exponential model, when the dose is low and $D\alpha << \beta$, this formula is approximated by a straight line (which also holds for the exact form involving ${}_1F_1()$), i.e.

$$P_{inf}(D \mid \alpha, \beta) \approx D\,\alpha / \beta.$$

For both $\alpha \to \infty$ and $\beta \to \infty$, while $\alpha/\beta \to r$, the Beta-Poisson formula converts into the exponential model.

Other assumptions for *n* or p_m lead to other models. For example, spatial clustering of cells in the inoculum can be represented by a negative binomial distribution or any other contagious distribution. However, this has little effect on the shape of the dose-response relationship (Haas, Rose and Gerba, 2014) although the limiting curve for the confidence interval is affected (Teunis and Havelaar, 2000). It is also possible to model p as a function of covariables, such as immune status or age.

Using these models, it is possible to determine the dose below which the dose-response relationship is linear (Williams, Ebel and Vose, 2011a). If the exposure distribution is such that doses will be below this value, then the risk characterization is greatly simplified.

14. Uncertainty / Variability

Variability and uncertainty are frequently confused because both can be described by distributions. However, they have distinct meanings (Haas, Rose and Gerba, 2014; Nauta, 2000; Vose, 2008), and a common understanding between the risk manager and risk assessor of these concepts can greatly help in the risk assessment process. These topics are considered below.

14.1 Variability

Variability, also sometimes referred to as inter-individual variability, refers to real differences in values of some property of the individuals from a 'population' over time or space. The population could refer to people, units of food, a species of foodborne pathogen, etc. Examples of variable factors relevant to microbiological risk assessment include (but are not limited to) the storage temperatures of food products, seasonality of different food preparation methods (e.g. barbecuing), culinary practice, susceptibility to infection across subpopulations, consumption patterns across a region, differences in growth and inactivation characteristics and in virulence between strains, and product handling processes across different producers.

In some cases, some of the variability in the population can be explained by observable individual attributes or explanatory factors. For example, while the human population is heterogeneous, there may be discernible differences between identifiable subpopulations because they are for some reason less frequently exposed, or less susceptible, to the hazard of interest. Or there could be different methods of storing a food product, e.g. frozen, chilled and not chilled, leading to different potential for microbiological growth; the fractions of the food item that are stored in each manner need to be known or estimated, and they may vary over time.

Hence, variability is inherent in the population being studied and describes by how much a specific attribute differs between the units in that population. As a result, variability cannot generally be reduced by more accurate measurement or more data points, it can only be estimated more precisely. However, some sources of variability may be explained by having more information, such as, knowing whether a food product was stored frozen, chilled or not chilled.

In principle, variability can be described by listing the different values that the attribute can take. Often however, there are such a large number of values that it is more convenient to describe the variation using a probability distribution. For example, if it is considered an animal shedding an enteric bacterial pathogen, then there are only two possible values, that is, the animal is shedding, or it is not. In contrast, if it is considered the number of bacterial cells in a 10 g faecal sample, then the possible values are 0, 1, 2, 3, etc. Instead of enumerating all possible values, and the probability with which these outcomes can occur, it is usually preferred (if possible) to describe the possible outcomes by a mathematical distribution, such as the Poisson or the negative-binomial distributions. The use of some mathematical distributions is quite well established for some circumstances, for example, the binomial distribution is usually used to describe the number of infected animals sampled from a large herd (or alternatively the hypergeometric distribution can be used for small herds). Similarly, the concentration of microbial cells in a sample is often assumed to follow a log-normal distribution, although others may be more appropriate (e.g. Bassett *et al.*, 2010; Haas, Rose and Gerba, 2014; Vose, 2008). Where possible, the fit of the mathematical distribution used to model a particular situation should be checked against empirical data. Tools for this include:

- Density histograms with fitted distributions overlaid;
- Cumulative distribution plots with fitted distributions overlaid;
- Quantile-quantile plots; and
- Skewness-kurtosis plot (Cullen and Frey, 1999).

When there are discernible differences due to known factors, 'stratification' can be a practical method of addressing the population variability by recognizing those populations as discrete within the risk assessment. The properties of each subpopulation, or stratum, may still be described as a variable quantity, but with a different mean and spread of values. There are many ways of stratifying a human population such as demographic, cultural and other variables, but in microbial risk assessment stratifications are usually done in one of two ways. One is based on differences in exposure and the other is due to differences in susceptibility, usually related to well recognised subpopulations such as the very young, old, pregnant and immune-compromised (YOPI). Exposure and sub-population strata may be combined, that is, within the population of interest, if there is evidence of differences in susceptibility or differential exposure patterns, then consideration should be given to stratifying the risk accordingly.

These ideas are illustrated in Figure 15. Here, it is assumed that exposure depends on season (A and B) and producer (1 and 2), leading to 4 different distributions of exposure (A1, A2, B1, B2). In addition, it is assumed that there are two subpopulations, each of which has its own dose-response curve. The figure shows how each exposure model is combined with the appropriate dose-response model if exposure and dose-response are stratified in this way.

Figure 15: Linkage between exposure assessment and hazard characterization

With respect to qualitative and semi-quantitative risk assessments, one option for the inclusion of variability is to consider a number of scenarios that reflect the variability, e.g. near-optimal condition, normal situation and one or more adverse conditions. The risk assessment then evaluates each as a separately measured risk scenario, and the results are compared. The overall assessment of variability (and also uncertainty) will be evaluated in narrative terms such as 'small', 'small', etc.

This approach will make the effects of variability on the risk estimate more transparent. However, if the scenarios vary greatly in risk outcome, such an analysis may provide insufficient support for decision-making in the absence of any description of the relative likelihood of each scenario. It should be noted that risk can be dominated by, or at least strongly influenced by, the more extreme scenarios, e.g. conditions leading to relatively high risk, despite their lower probability. It is important that the risk assessor identifies the likelihood with which such scenarios could occur.

14.2 Uncertainty

Uncertainty arises due to a lack of knowledge and is sometimes termed epistemic uncertainty, lack-of-knowledge uncertainty, or subjective uncertainty. It is often stated that variability is a property of the system being studied, whereas uncertainty is a property of the methodology and data used. Assessments with different methodologies and data, etc. will have different levels of uncertainty regarding their outputs. An understanding of uncertainty is important because it provides insight into how the lack of knowledge can influence decisions. In the EFSA opinion on the principles and methods behind EFSA's Guidance on Uncertainty Analysis in Scientific Assessment (EFSA, 2018a) uncertainty is used as a general term referring to all types of limitations in available knowledge that affect the range and probability of possible answers to an assessment question. Available knowledge refers to the knowledge (evidence, data, etc.) available to assessors at the time the assessment is conducted and within the time and resources agreed for the assessment. When the uncertainty is large enough that there is ambiguity as to which risk management decision is preferred, then there may be value in collecting additional data or conducting additional research to reduce the uncertainty; it is the risk managers' role to decide if the uncertainty of a risk assessment output allows for a decision to be made or not. These aspects apply equally to all parts of the qualitative-to-quantitative continuum of risk assessment.

In contrast to variability, uncertainty is not inherent in the population, but a result of limited information and our lack of knowledge. Consequently, well targeted collection of data or information can usually help reduce uncertainty. For example, the uncertainty in the parameter estimates from a linear regression model can be reduced when more data from the same population can be incorporated into the model fit. Similarly, uncertainty in the processing practices used to manufacture a food product can be reduced by visiting different manufacturing facilities (of different sizes) to gain a better of what actually happens in practice.

Uncertainty is associated not only with the inputs to an assessment model, but also regarding the scenarios assumed for the assessment and the model itself. Sources of scenario uncertainty include potential misspecification of the harmful agents of concern, exposure pathways and vectors, exposed populations, and the spatial and temporal dimensions of the problem.

Sources of model uncertainty include model structure, detail, resolution, validation or lack thereof, extrapolation, and boundaries of what is included and what is excluded from the model. A list of most common types of uncertainty affecting scientific assessments associated with the inputs and the methodology was identified by EFSA (2018a) and these are presented in Table 40. In addition, Morgan and Henrion (1992) and Cullen and Frey (1999) provide examples of sources of uncertainty in risk assessment.

Table 40: List of most common types of uncertainty affecting risk assessments associated with the inputs and the methodology (EFSA, 2018a).

Uncertainties associated with assessment inputs	Uncertainties associated with assessment methodology
Ambiguity	Ambiguity

Accuracy and precision of the measures	Excluded factors
Sampling uncertainty	Distributional assumptions
Missing data within studies	Use of fixed values
Missing studies	Relationship between parts of the assessment
Assumptions about inputs	Evidence for the structure of the assessment
Statistical estimates	Uncertainties relation to the process for dealing with evidence from the literature
Extrapolation uncertainty (i.e. limitations in external validity)	Expert judgement
Other uncertainties	Calibration or validation with independent data
	Dependency between sources of uncertainty
	Other uncertainties

14.3 Uncertainty Analysis

Uncertainty analysis is the process of identifying limitations in scientific knowledge and evaluating their implications for scientific conclusions (EFSA, 2018b). It is therefore relevant in all risk assessments to ensure that the conclusions provide the risk managers reliable information for decision making. The form and extent of uncertainty analysis, and how the conclusions should be reported, vary widely depending on the nature and context of the assessment and the degree of uncertainty that is present.

In a Guidance on Uncertainty Analysis (EFSA, 2018a) EFSA presented the main elements of an uncertainty analysis as the following:

1. Identifying uncertainties affecting the assessment.
2. Prioritising uncertainties within the assessment
3. Dividing the uncertainty analysis into parts.
4. Ensuring the questions or quantities of interest are well-defined.
5. Characterising uncertainty for parts of the uncertainty analysis.
6. Combining uncertainty from different parts of the uncertainty analysis.
7. Characterising overall uncertainty.
8. Prioritising uncertainties for future investigation.
9. Reporting uncertainty analysis.

Identifying the various uncertainties affecting the risk assessment outputs is necessary in every assessment and should be done in a structured way to minimise the chance of overlooking relevant uncertainties. Although it is often efficient to concentrate detailed analysis on the most important sources of uncertainty, the identification of uncertainties needs to be as comprehensive as possible. Risk assessors should examine in a systematic way every part of their assessment in order to identify all uncertainties, including those related to the inputs of the assessment as well as the methods used in the assessment (see Table 40 above).

Prioritising uncertainties within the risk assessment plays an important role in planning the uncertainty analysis, enabling the assessor to focus detailed analysis on the most important uncertainties and address others collectively when evaluating overall uncertainty. Prioritisation can be done by expert judgement during the planning process. In more complex risk assessments

uncertainties can be prioritized explicitly using sensitivity analysis (see Chapter 15). Depending on the methods and data used, it may be sufficient to characterise overall uncertainty for the whole assessment directly, by expert judgement. In other cases, it may be preferable to evaluate uncertainty for some or all parts of the assessment separately and then combine them to evaluate the overall uncertainty, either by calculation or expert judgement.

Each parameter of interest must be well-defined. This is necessary to ensure the parameter can be estimated appropriately and to make it possible to express uncertainty clearly and unambiguously.

Sometimes risk assessors choose or need to divide the uncertainty analysis into parts. In these cases, there may be a need to combine the different parts of the uncertainty analysis if an overall estimate of uncertainty is needed.

The element of overall uncertainty characterization includes the quantitative expression of the overall effect of as many as possible of the identified uncertainties on the conclusions and the qualitative description of any uncertainties that remain unquantified. In assessments where the impact of one or more uncertainties cannot be characterised, it must be reported that this is the case and that conclusions are conditional on assumptions about those uncertainties; these assumptions also need to be specified.

Prioritising uncertainties for future investigation is implicit or explicit in any assessment where recommendations are made for future data collection or research; these priorities may be informed by the sensitivity analysis.

The last step of the uncertainty analysis process is reporting. Uncertainty analysis is part of the risk assessment and should be reported in a transparent manner. It is important to list the sources of uncertainty that have been identified and document how they were identified, how each source of uncertainty has been evaluated and how they have been combined, where and how data and expert judgement have been used, what methodological approaches have been used and the rationale for choosing them, and what the results were.

It is not necessary to use all the above elements in uncertainty analysis of all risk assessments. The extent and depth of the uncertainty analysis can be scaled to the needs of the assessment and the time and resources available. In addition, the approach to each element, as well as the order in which they are conducted, may vary depending on the nature or type of each risk assessment.

14.4 Uncertainty and variability together

Most risk assessments will contain variable and uncertain inputs. In some cases it may be difficult to decide whether information relates to uncertainty and/or variability. When model parameter estimates from the scientific literature are expressed as a mean value with an associated standard deviation, it may be unclear whether this standard deviation is an expression of variability or uncertainty, or both. For example, when a growth rate is estimated from a set of growth experiments, it may not be clear whether the standard deviation in the growth rate (usually referred as a *standard error*, to denote that it refers to an estimate of a parameter) expresses uncertainty or variability. It is not sure if the growth rate is actually fixed, but cannot be determined precisely by growth experiments, or varies between the experiments but can be determined precisely. Presumably, the standard deviation expresses both. In practice, it may be important to know which characteristic is represented, and to what extent (Nauta, 2000).

When it is unclear how uncertainty and variability should be separated, there are several possible ways to proceed:

- One could test the effect of separation, assuming different 'weights' (i.e. proportional contributions) for uncertainty and variability and exploring the effect on the model outputs in several scenarios (e.g. Nauta, 2000). This will show how important it is to separate uncertainty and variability in the given situation.
- Alternatively, one might first assume that uncertainty is absent. An assumption of omniscience (pretending that everything is known) results in the remaining probability distributions necessarily describing variability. Once the variability is identified, uncertainty can then be reintroduced through scenarios by systematically varying the uncertain inputs and observing their effect on the model outputs. This approach may be quite cumbersome if there are many uncertain model inputs.
- Another way to access the potential effect of uncertainty is to identify the variable components, set their uncertain parameters to their expected value and run the model (similar to the approach described in the previous bullet point). Then the model is run as a 'mixed' model where the uncertain and variable components are simulated together using distributions as inputs. The results of the two models can then be compared to assess the potential effect of uncertainty on the model outputs and the need or otherwise to separate the two by developing a second order model.
- Cullen and Frey (1999) suggest that the relative importance of variability and uncertainty can be assessed by inspection of a two-dimensional simulation result plotted in the form of a cumulative distribution function (CDF) with confidence intervals. The mean CDF is a best estimate of variability. The confidence interval on the CDF is a best estimate of uncertainty. If the intervals are wide compared to the range of variation of the best estimate CDF, then uncertainty dominates. If the intervals are narrow, then variability dominates.
- Alternatively, Thompson and Graham (1996) provide an overview of when to select various probabilistic analysis methods depending on the policy analysis objectives.

In practice, a combination of the above approaches may be needed. For example, while uncertainty in parameter estimates can be assessed using a two-dimensional simulation model, differently structured food supply pathways may need to be assessed through different scenarios.

To illustrate the effects of variability and uncertainty consider the following situations. In the simplest case, the risk measure may be a single point probabilistic measure, e.g. the probability of at least one illness per year or the expected number of cases per year (i.e. no variability was included). This means that, if no uncertainty has been included in the risk assessment model, then the outputs are fixed values (Figure 16, top left). If uncertainty has been included in the model, then the outputs are uncertainty distributions (Figure 16a).

The risk measure may alternatively be a probability distribution capturing variability, e.g. a probability distribution of the number of adverse health events a random person might experience per year. This will be a first-order distribution if no uncertainty has been included in the model (Figure 16b), or if uncertainty and variability have been combined. If uncertainty has been included in the model and not combined with variability, then the output will be a second-order probability distribution (Figure 16c).

Thirdly, the risk measure may describe the variation in risk across a population, e.g. in different strata. That risk can, for example, be characterized as the probability of illness per serving. It can be ended up with a distribution of the variability in that probability across strata (see Section 14.1). The results can then also be stratified by graphing the variation in that probability per serving for each stratum. If the risk assessment did not include uncertainty, a single probability measure could be

used to describe the risk for each stratum (Figure 16d). If the risk assessment included uncertainty (not combined with variability), then it can be also looked at how sure about these estimates of probability per serving (Figure 16e). It is difficult to graphically compare more than two second-order distributions so, whilst it is theoretically possible to produce, for example, probability distributions of the number of illnesses per stratum over a period, if these are second-order distributions it will generally be clearer to make a comparison of an appropriate statistic (mean, 90th percentile, etc.) with attendant uncertainties.

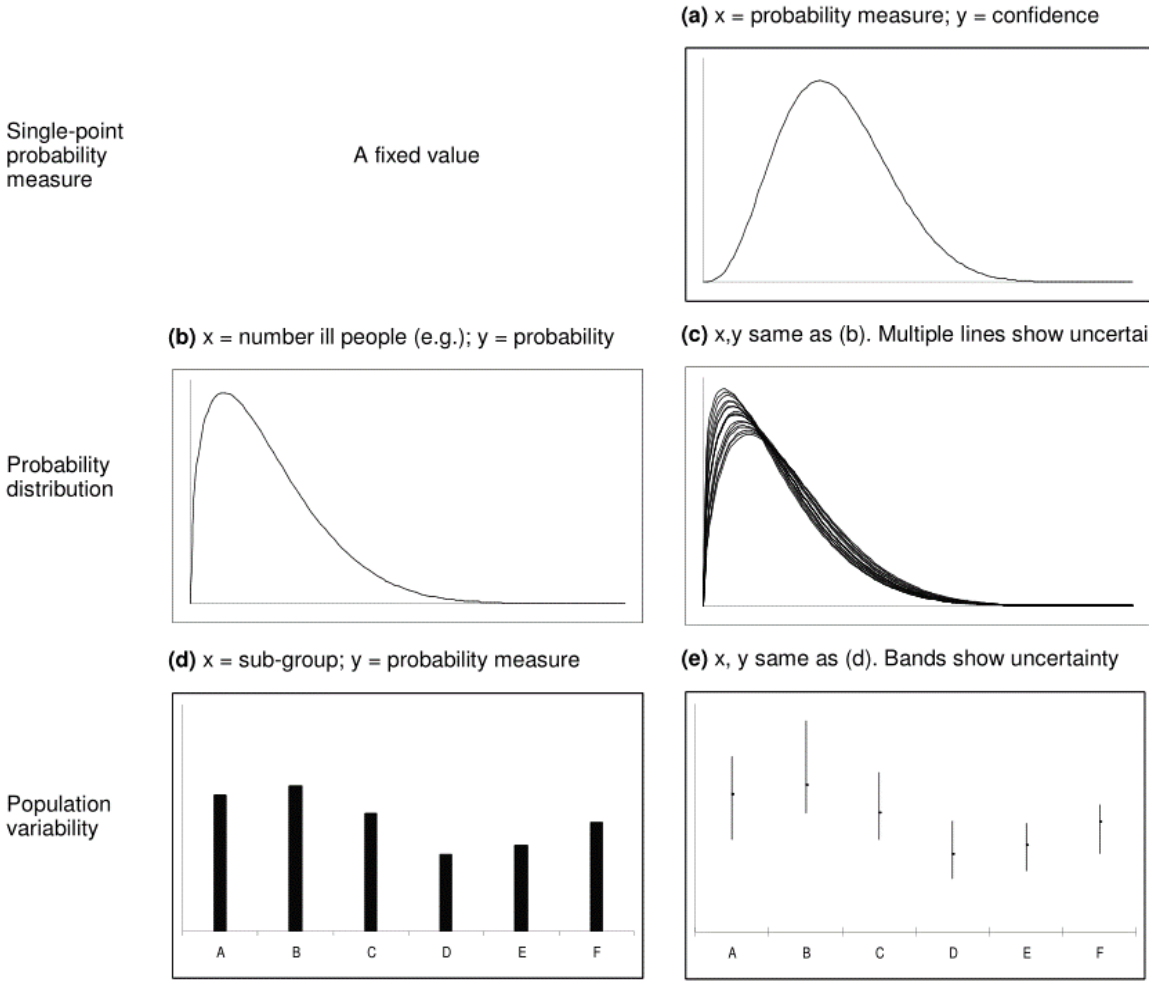

Figure 16: A matrix of various types of quantitative outputs one can produce from a risk assessment describing variability and uncertainty; variability only is shown in the graphs on the left and uncertainty and variability combined are shown in the graphs on the right.

To separate variability and uncertainty using Monte Carlo analysis, one can apply second order, or two-dimensional Monte Carlo techniques. In 'one-dimensional' simulation modelling the random realizations of the model inputs can be thought of as being arranged in a one-dimensional vector, with length equal to the number of iterations used for the model. In contrast, the two-dimensional approach can be considered as a series of such vectors, making a two-dimensional array or matrix of size ($N_v \times N_u$); the row dimension (N_v) then captures the variability in the input while the column dimension (N_u) captures the uncertainty (see Figure 2 in Pouillot *et al.*, 2007; and Figure 6 in Pouillot and Delignette-Muller, 2010). It should be noted that two-dimensional modelling is not a necessity for dealing with variability and uncertainty. In fact, "manually" investigating uncertainty and variability using for example scenario analysis can be more informative than "blindly" applying second order modelling.

15. Sensitivity analysis

Complex risk assessments may have many input and output variables that are linked by a system of equations or other model structures. Sensitivity analysis is a broad set of tools that can provide insights to risk assessors and risk managers about the relative importance of the components of a risk assessment to the risk management question (Frey, Mokhtari and Danish, 2003; Frey, Mokhtari and Zheng, 2004; Saltelli, Chan and Scott, 2008). The plausibility of important components is essential to the overall quality of the risk assessment. Changes in important components also can be expressed in terms of the influence that these inputs have on the answers to risk-management questions.

A key criterion for sensitivity analysis is that it must be relevant to a decision. Sensitivity analysis evaluates the effect of changes in model input values and assumptions on the model output, and thus on decisions that would be based on the model output. It can be used during model development to evaluate and refine model performance and can play an important role in model verification and validation. Sensitivity analysis can also be used to provide insight into the robustness of model results when making decisions.

Sensitivity analysis can also be used as an aid in identifying risk mitigation strategies or monitoring points and to focus research activities for purposes of prioritizing additional data collection or research. For these purposes, *Value of Information* (Laxminarayan and Macauley, 2012) analysis can complement sensitivity analysis methods, because the return to risk management decision-making on research and data collection expenditures depends on a variety of additional considerations, e.g. cost and time.

Microbiological risk assessment models typically have the following characteristics, which can pose substantial challenges to the application of sensitivity analysis methods:

- non-linearities;
- thresholds, e.g. below which there is no growth of a microbiological pathogen;
- discrete inputs, e.g. integer numbers of animals or ‘yes’ or ‘no’ indicators of contamination;
- incorporation of measurement error;
- variation in the scale (units and range) and shape of distributions of model inputs; and
- temporal and spatial dimensions, including dynamics, seasonality or inter-annual variability.

The relationship between model inputs and outputs should be one-to-one for effective application of sensitivity analysis methods. Ideally, a sensitivity analysis method should provide not just a rank ordering of key inputs, but also some discriminatory quantitative measure of sensitivity, such that it is possible to clearly distinguish the relative importance of different inputs (e.g. correlation). For example, are there groups of inputs among which several inputs are of comparable importance, and is there clearly a difference in importance between such groups? Statistical-based methods such as regression analysis or analysis of variance (ANOVA) produce quantitative indicators of the relative importance of different inputs, e.g. using normalized or standardized regression coefficients. Moreover, techniques such as regression analysis also provide an indication of the statistical significance of differences in sensitivity among inputs, based on confidence intervals for regression coefficients, e.g. a statistically non-significant model input implies that the model input does not have an effect on the model output. However, it should be noted that statistical tests may be able to detect very small effects, especially if the number of iterations is large, and hence any significant effect should be assessed as to its practical importance, i.e. is the effect large enough to affect risk management?

This section emphasizes sensitivity analysis in quantitative risk assessment models, although some of the techniques, e.g. exploratory methods, may apply to both quantitative and qualitative assessments.

15.1 Sensitivity analysis in qualitative risk assessment

In examining an association between a hazard and an adverse health effect, widely accepted criteria (e.g. Hill's Criteria of causation) have been established for determining whether the evidence is weak, moderate or compelling (e.g. Tomatsis, 1990). Narrative criteria may be inherently subjective, and therefore difficult to reproduce. To the extent that the criteria can be evaluated objectively, however, different assessors using the same information should be able to independently reproduce a determination of whether the criteria have been satisfied. For example, the weight of evidence for causality is stronger if detection of the association has been independently reported from multiple sources, if the strength of association is related to the level of exposure to the agent, or changes in the hazard precede changes in the observed effect. Determining whether such criteria are satisfied is evidence-based. If the results of a qualitative assessment are invariant to an accumulation of evidence regarding an association or, alternatively, to contradictory evidence, then the assessment is insensitive to the established criteria for evaluating causality. For example, in a qualitative hazard characterization, an assessment based solely on the criteria of acute health outcomes could be insensitive to information regarding known chronic sequelae. Alternatively, a qualitative hazard characterization may be highly sensitive to weak evidence regarding chronic sequelae associated with an opportunistic pathogen that rarely causes acute illness. If a qualitative risk assessment finds that a pathogen poses a negligible risk based on the assumption that the pathogen does not grow under certain environmental conditions, and new information indicates that the pathogen is capable of growing under these conditions, then the sensitivity of the findings of the risk assessment to this new information may depend on prespecified criteria, e.g. have the results been independently reproduced? Have the methods been exposed to peer review? At a minimum, the scientific basis and criteria for characterization of a qualitative risk assessment need to be sufficiently transparent to permit assessment of the effect of new information or plausible alternative assumptions on the findings.

15.2 Sensitivity analysis in quantitative risk assessment

There are several approaches to sensitivity analysis in quantitative risk assessment models. Saltelli *et al.* (2008) provide a thorough exploration of the topic, summarized below, as do Frey *et al.* (2003; 2004).

15.2.1 *Statistical methods*

Examples of statistical sensitivity analysis methods (also referred to as variance-based methods) include rank order correlations, regression analysis, ANOVA, response surface methods, Fourier amplitude sensitivity test (FAST), mutual information index (MII), and classification and regression trees (CART) (Frey, Mokhtari and Danish, 2003; Frey, Mokhtari and Zheng, 2004; Frey and Patil, 2002; Mokhtari, Frey and Jaykus, 2006). Most of these methods are applied in conjunction with, or after, a Monte Carlo simulation. Regression analysis, ANOVA, FAST and MII provide quantitative measures of the sensitivity for each input. Regression analysis requires the assumption of a model form.

15.2.2 *Graphical methods*

Graphical methods represent sensitivity typically in the form of graphs, such as scatter plots and spider plots (Eschenbach, 1992; Frey, Mokhtari and Danish, 2003). The results of other sensitivity analysis methods also may be summarized graphically, e.g. tornado charts for displaying rank order

correlation. These methods can be used as a screening method before further analysis of a model, or to represent complex dependencies between inputs and outputs. For example, such complex dependencies could include thresholds or non-linearities that might not be appropriately captured by other techniques.

15.2.3 *Evaluation of sensitivity analysis methods*

Each sensitivity analysis method provides different information (e.g. Table 5-1 in Frey, Mokhtari and Zheng, 2004) regarding sensitivities of the inputs such as the joint effect of inputs versus individual effects, small perturbations of inputs versus the effect of a range of variation, or apportionment of variance versus mutual information. Because agreement among multiple methods implies robust findings, two or more different types of sensitivity methods might be applied where practicable, to compare the results of each method and draw conclusions about the robustness of rank ordering of key inputs. Non-parametric methods, such as Spearman's rank correlation, are applicable to monotonic, non-linear models. Vose (2008) recommends the use of spider plots to illustrate the effect of individual input variables on the uncertainty of the model output.

16. Quality Assurance

The validity of any risk assessment is based on the soundness of the model structure, its inputs, the underlying assumptions and the interpretation of results. Therefore, quality assurance is a crucial element of risk assessment.

16.1 Data evaluation

Risk assessors must evaluate the quality of the data used in the analysis (see also Chapter 10), and the means of characterizing the uncertainty of any data used. The aspects listed in this section are not primarily intended for differentiating "good" from "bad" data, but rather to guide the subsequent analysis and their use in a risk assessment model.

Formalized quality control of raw data and its subsequent treatment is desirable, but also dependent on data availability and how the data are used. There is no formalized system for evaluation of data. Few generalizations can be made, but the means by which data are collected and interpreted needs to be clear. "Good" data are complete, relevant and valid: complete data are objective; relevant data are case-specific; and validation is context specific.

Data which are complete include such things as the data source and the related study information (e.g. sample size, species or strain, immune status, etc.). Characteristics of relevant data can include age of data; region or country of origin; purpose of study; analytical or data collection methods. Observations in a database should be "model free", i.e. reported without interpretation by a particular model, to allow data to be used in ways that the original investigator might not have considered. Ideally this implies that the raw data can be accessed, which may be difficult to achieve in practice. Scientific publishers are encouraging the sharing of data associated with publications, where possible, and independent data repositories have also been created; see for example http://foodrisk.org or https://www.combase.cc.

Valid data are those that agree with others in terms of comparable methods and test development. In general, for dose-response modelling, for example, human data need less extrapolation and are preferred to animal data, which in turn are preferable to in vitro data. Data on the pathogen of concern are preferred to data on surrogate organisms, which should only be used when proven to be valid (NACMCF, 2010).

The current recommended practice is to consider any available data as potentially useful. Whether data should be eliminated from the risk assessment depends on the purpose and stage of the assessment. Small data sets or those with qualitative values may be useful in the early stages of a risk assessment. The later stages of risk assessment may include only those data that meet a particular quality standard. Excluding data from the analysis should be based on predefined criteria, e.g. age of the data set, geographic representativeness, etc., and not based solely on statistical criteria (e.g. Section 16.1.2). If the data are extremely heterogenous or contain outliers, they may be stratified according to suitable criteria. This practice should provide increased insight rather than information loss.

Sources of data may come from the peer-reviewed or non-peer-reviewed literature. Although peer reviewed data are generally preferable, they also have some important drawbacks (see also Section 10.1). Access to the peer reviewed literature may be restricted especially for developing countries, although open-access publications and Research4Life (see Section 3.5.2), for example, are helping to address some of these limitations. Peer reviewed data may be missing important methodological details (e.g. sample preparation and characteristics), are usually presented in an aggregated form, and may not provide the level of detail necessary for uncertainty analysis. Quality control of the

measurement process may be poorly documented. The potential for publication bias should not be ignored, as 'replication studies' may not provide enough novelty for publishers and hence may only get published through conference presentations, reports or other formats. The analyst might wish to add information from other sources for any of these reasons. The quality of any data used should be explicitly reviewed, preferably by independent experts, and any concerns regarding data quality should be explicitly noted.

The results of any risk assessment are conditional on the data and information used to develop the risk model. Any risk assessment should summarize the primary strengths and limitations of the data, methods, and analyses used. Typically, these analyses require risk assessors to synthesize and draw inferences from disparate data sources not specifically or originally intended for use in risk assessment. In some cases, this requires the use of unconventional or non-routine methods that might be highlighted for close scrutiny, to ensure that they are reasonable and correctly applied.

16.1.1 *Data collection*

Suitable data for microbiological risk assessment may be sparse. Assessors should initially collect all reasonably obtainable data consistent with the assessment objective, and subsequently investigate the quality of different data sources. When collecting data for input distributions, several issues should be considered to evaluate data quality. The following considerations apply to any data, including information elicited from experts.

Risk assessors should ideally have access to raw, un-summarized data (e.g. EcoSure, 2008). Statistical methods such as quantile-quantile plots and skewness-kurtosis plots (Cullen and Frey, 1999) can be useful to identify suitable parametric distributions, if the raw data contain sufficient observations. Alternatively, empirical distributions or non-parametric simulation methods can be used to characterize input distributions. Graphical methods are generally preferred over statistical tests (e.g. Goodness-of-Fit) which are affected by the size of the data set. Large sample sizes can identify statistically significant deviations from the hypothesised distribution, even though these deviations may be of little practical importance.

Raw data are frequently inaccessible and results are often reported as aggregated summary statistics (e.g. estimated mean, standard deviation or standard error). It may be necessary to obtain information on the assumed distribution of the underlying data, together with the sample size to develop a distribution from data summary statistics.

It is useful to collect as much background information on the data sources as possible, such as the year of completion, country of origin, the type of sample, possible transformation of the data, methods of analysis, microbiological strain and population demographics. This information could be important about treatment or use of the data or to support the decision on whether to include these data in the model. An example is given below.

This example is from a Danish risk assessment for *Campylobacter jejuni* in chicken (Christensen *et al.*, 2001). Quantitative data were needed to describe the relative change in pathogen concentration over a given step in a poultry slaughterhouse. Data from foreign studies were applied to assess the efficacy of the wash and chiller process in reducing the pathogen levels on chicken carcasses because Danish data were unavailable. Data for the microorganism of interest were available, but the data were obtained from different sample units (neck skin samples, whole carcass wash, and swab samples). This mix of sample types all reflected surface contamination of chicken carcasses. The risk assessors assumed that the relative reduction in pathogen concentration over the process was independent of the type of surface measure. The slopes of the lines shown in Figure 17 reflect

differences in log-concentration over the process. Since all the slopes appear to be similar (though not identical), all data sets were used in describing the reduction over the 'wash + chiller' process.

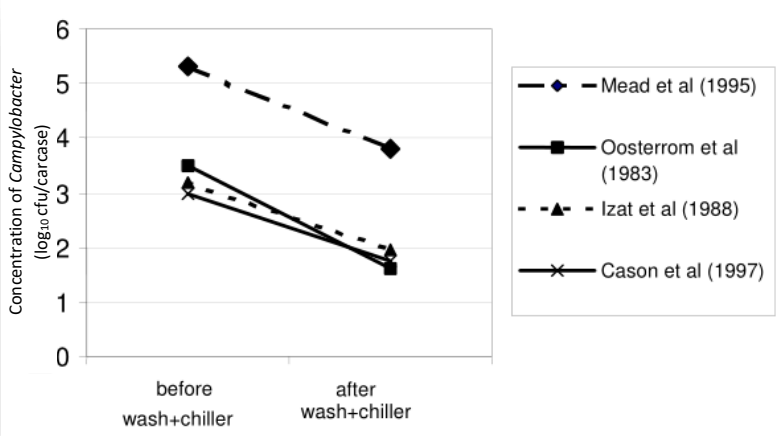

Figure 17: The influence of a selected slaughterhouse process on the Campylobacter concentration on chicken carcasses. The change in pathogen concentrations (expressed as log CFU per carcase) before and after the process is represented by a line connecting data points originating from the same study.

Data for the specific microorganism under study may not always be available or of suitable quantity and quality. Data from a surrogate microorganism may be used, provided that the surrogate behaves similarly under the process of interest, e.g. generic *E. coli* to estimate cross-contamination during slaughter procedures. Data from different surrogate organisms could be used to model different steps in the same model, based on data availability and suitability. Sampled data with different units, e.g. absolute concentration or change in concentration, can be used to describe the same process, as the example above illustrates. Depending on how the data are used in the model, e.g. describing a change in concentration over a step or describing the concentration level, different parameters may be evaluated in a sensitivity analysis to ensure data quality objectives are satisfied.

In some cases, the available data may not be representative of the population of interest. These data may be excluded from the analysis or incorporated with appropriate adjustment. The bases for decisions regarding the treatment of non-representative data are context specific and need to be clearly articulated. For example, data from a particular source may be considered non-representative for the purposes of providing an estimate of central tendency (e.g. the mean) but may nevertheless be useful for the purposes of characterizing the spread of an input distribution (e.g. plus or minus an order of magnitude).

16.1.2 *Sorting and selecting data sources*

After collecting potentially suitable data sets, the risk assessor should evaluate each critically and select the data that will provide the most appropriate model input for the specific purpose (e.g. contamination level, contamination prevalence or changes during processing). Plotting the parameter of interest with the 95% confidence intervals provides a useful overview (see Figure 18).

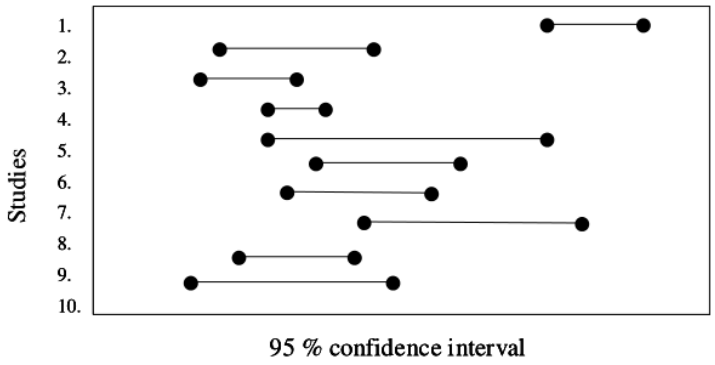

Figure 18: Example of an overview of data from different studies, with model input parameter 95% confidence intervals.

Both subjective and statistical criteria may be applied in selecting the suitable data sets for incorporation into the risk assessment. Subjective evaluation criteria may include the representativeness of the geographical and temporal properties of the study. If study 1 in Figure 18 is the only study conducted outside the country of interest, and it is significantly different from the rest (based on statistical criteria), this data set could be excluded. If the 10 studies all originate from the same country, but are reported by different laboratories, the differences may be due to variability between the laboratories or specific sampling context and the assessor might decide to incorporate all studies in the model. Irrespective of the decision taken, the rationale should be documented.

16.2 Model Quality Assurance

Models should be both verified and validated and may also be anchored (calibrated). Model verification is achieved by auditing the model to ensure that it operates as intended by the developer. Anchoring and calibration are techniques to adjust the model to approximate observed data. Model validation can be defined as demonstrating the accuracy of the model for a specified use. Model verification should precede model validation. If the model is to be both anchored and validated, using a withheld test portion of the independent data, then anchoring should precede model validation.

16.2.1 *Model verification*

Verification includes checking of the software code used to implement the model. Verification requires that the model be suitably documented. All data, methods, assumptions and tools used should be clearly described, so that the model can be independently reproduced. A well-organized model structure facilitates verification.

The following questions may be useful for those seeking to verify a model:

- Are the analytical equations correctly derived and free of error? If approximations are used, then under what assumptions do they hold and are those assumptions always met?
- Is the computerized version of the analytical model correctly implemented? What, if any, are the limits of the implementation?
- Are the inputs correctly specified?
- Do the units of measurement (e.g. CFU or log CFU) propagate correctly through the model?
- Is the model internally consistent? For example, if an assumption is made in one part of the model, is it consistently applied throughout the model? Is there consistency within the model between the intermediate outputs and inputs?

- Are errors in any computational step flagged appropriately, or could they result in inappropriate values being propagated through the model?
- Are the intermediate outcomes and end results evaluated to be realistic?

It may be difficult in some cases to do a line-by-line verification of computer code, especially for large models. The verification of any computer code will be facilitated if good software engineering practices (e.g. Pressman, 2005) are followed, including clear specification of databases, development of a software structure design prior to coding, version control, modular design, clear specification of interfaces between components of a model, and good communication among project teams when different individuals are developing different components of a model. Literate programming techniques (Knuth, 1992) can also be useful for this purpose as they allow embedding of the model code in the documentation; a range of tools for various programming languages and environments are available.[22] Model documentation and peer review are critical aspects of the verification process.

16.2.2 *Model anchoring or calibration*

Anchoring is a technique in which the model is adjusted, or calibrated, to be more compatible with observed data. For example, model parameters may be adjusted to achieve agreement between model predictions and observed data, e.g. predicted versus actual number of illnesses per year attributed to the hazard and the food. As noted above, if the model is to be both anchored and validated, using a withheld test portion of the independent data, then anchoring should precede model validation.

Anchoring is a generally accepted practice in health risk assessment and environmental modelling, and has been employed in one fashion or another in various risk assessments (CFSAN and FSIS, 2003; FAO/WHO, 2005; FSIS, 2001, 2005). Data from outbreaks could be considered as the ultimate 'anchor' for dose-response models and are also an important way to validate risk assessments. This is because the dose ingested by different consumers involved in an outbreak is likely to be more similar than the doses associated with sporadic cases. Since anchoring requires some data, it may compromise efforts to validate the model in situations without sufficient data to support both activities. A common approach in statistics and machine learning (e.g. neural networks, etc.) is to separate a data set into two independent components: training and test data. The training data are used to fit the model and estimate the model parameters, while the test data are used to independently check the predictions of the model against previously unseen observations. In general, anchoring approaches that weigh model inputs in proportion to their likelihood in light of the observed data are superior to using simple adjustment factors or censoring input values that are incompatible with the observed data (NAS, 2002; Williams, Ebel and Vose, 2011b). Whatever the anchoring approach, considerable care must be taken to ensure that the adjustment procedure is well reasoned and transparent.

16.2.3 *Model validation*

Model validation can be defined as demonstrating the accuracy of the model for a specified use. Accuracy is the absence of systematic and random error, commonly known as trueness and precision, respectively. Models are always incomplete representations of the system they are intended to model, but they can still be useful. General information on working with mathematical models can be found in various theoretical and applied textbooks. Doucet and Sloep (1992) give a good introduction to model testing. These authors discriminate between models shown to be worthy of our belief (i.e. plausible) and models shown to be true. McCullagh and Nelder's book on generalized linear models (1989) is a valuable resource on statistical modelling methods, and

[22] https://en.wikipedia.org/wiki/Literate_programming accessed 5 December 2018

describes some general principles of applying mathematical models, underlining three key principles: (i) All models are wrong, but some are more useful than others; (ii) Do not fall in love with one model to the exclusion of others; and (iii) Thoroughly check the fit of a model to the data.

Law (2014), in addressing the issue of building valid, credible and appropriately detailed simulation models, considers techniques for increasing model validity and credibility. Model validation procedures should be aimed at answering questions like: (i) Does the model make sense; (ii) Does the model respond in an appropriate manner to changes in input assumptions; and (iii) Do predictions respond in an appropriate manner to changes in the structure of the analysis? These processes are also referred to by some as a 'reality check', 'laugh test' or 'confidence building'.

Model validation is highly dependent on the risk-management question, and the degree of validation required should be proportionate to the stakes of the decision. Model validation involves demonstrating the accuracy of the model for a specified use and there are different aspects to model validation. Dee (1994, 1995) identified four major aspects associated with model validation: (i) Conceptual validation; (ii) Validation of algorithms; (iii) Validation of software code; and (iv) Functional validation. These are described below.

Risk assessment, like any type of problem solving is cyclical in nature. Defining the problem, considering alternative solutions, and implementing a solution all lead to the need to assess the effectiveness of the chosen solution. The cycle may repeat based on that assessment. No risk assessor should think their job is done after a risk management decision is made. The risk assessor may begin planning how they will assess the validity of the predictions of their model in the context of the risk management option selected. This assessment of validity may not occur until years after risk management options are implemented.

Conceptual validation concerns the question of whether the model accurately represents the system under study. Was the simplification of the underlying biological process in model steps realistic, i.e. were the model assumptions credible? Usually, conceptual validation is largely qualitative and is best tested against the opinion of experts with different scientific backgrounds. Different models with various conceptual bases can be tested against each other within a Bayesian framework, using Bayes factors, or some other information criterion (Kass and Raftery, 1995). Experimental or observational data in support of the principles and assumptions should be presented and discussed. With respect to dose-response modelling, the concepts described in Section 6.3 are a minimum set of assumptions representing the consensus opinion of a broad group of experts who contributed to the original FAO guidelines on hazard characterization (FAO/WHO, 2003). These are based on mechanistic reasoning and are supported by some experimental evidence. As such, they are considered to be currently the best basis for dose-response modelling studies.

Algorithm validation concerns the translation of model concepts into mathematical formulae. It addresses questions such as: Do the model equations represent the conceptual model? Under which conditions can simplifying assumptions be justified? What effect does the choice of numerical methods for model solving have on the results? and: Is there agreement among the results from use of different methods to solve the model?

Software code validation concerns the implementation of the model in a computer language. Good programming practice (i.e. modular and fully documented) is an essential prerequisite. Specific points for attention are the possible effects of machine precision and software-specific factors on the model output. For this reason, open-source software and models implemented in a computing language (e.g. R, Python, C++, etc.) may be preferable to those implemented in a proprietary

software program, as all computational steps can be inspected if needed. Internal error reports of the software are important sources of information, as well as evaluation of intermediate output.

Functional validation concerns checking the model against independently obtained observations. Ideally, it is evaluated by obtaining pertinent real-world data, and performing a statistical comparison of simulated outcomes and observations (Ebel and Williams, 2019). This requires more detailed information than is usually available, especially if data are also used for anchoring (Section 16.2.2). It may be possible to compare results from risk assessment studies with independently obtained epidemiological estimates of disease incidence. Such data cannot validate a dose-response model *per se* but may produce valuable insights, especially if the predictions do not closely match epidemiological observations. Most studies to date have considered that a range check of estimated risks and observed incidences was sufficient "validation" of the model.

Credibility of results can also be established by demonstrating that different sources of data are consistent with output values. These might include intermediate outputs. Cassin *et al.* (1998) provide a good example of such comparisons. When making such comparisons, the different nature of vehicle, microbiological hazard and processes must be accounted for. It should be noted that if the model output does not agree with the observations, it might not necessarily be that the model is wrong. It may be that the observation itself was influenced by an unknown factor (e.g. microbiological methodological insensitivity) or the underestimation of foodborne illness associated with current epidemiological data. There may also be a variety of different influences acting in concert to cause the differences in the results.

Close agreement between an initial risk-modelling effort and independent validation data would be fortuitous. Agreement between the model output and validation data may be coincidental, however, and would not necessarily indicate that all of the intermediate model components are accurate. Typically, model development and refinement are iterative. Whether model validation or anchoring is considered, the credibility of the model may be strengthened by having multiple points at which the model can be compared to observed data. In general, the scientific credibility of a model is strengthened if consistent results are derived from different relevant data sources (e.g. laboratories, regions) or types (observational or experimental), or a combination. The required degree of relevance and consistency is a context-specific judgement. The tolerance for inconsistent answers depends on what constitutes an 'important' difference with respect to changes in model results. In the risk assessment context, an important difference in model results is one that would significantly modify the risk management decision under the relevant decisional criteria.

There are situations in which it may be difficult, or practically impossible, to completely validate a model. For example, because risk assessment models are often attempting to predict low probability events, it can be difficult to obtain an independent data set of sufficient sample size to make a sensible comparison of predictions versus observations. It may be possible to validate components of the model even in such situations. For example, it may be possible to validate portions of the model that deal with a particular exposure pathway by making measurements of contaminant levels in specific foods.

In many cases, there may be insufficient or no independent data with which to compare model predictions. In these situations, alternatives to validation include: (i) Screening procedures to identify the most important model inputs and pathways; (ii) Sensitivity analysis to identify the most important inputs or groups of inputs; (iii) Uncertainty analysis to evaluate the effect of uncertainty in model inputs with respect to predictions; (iv) Comparison among predictions of different models;

and (v) Evaluation of sensitivity of results to different assumptions regarding scenarios, model boundaries, model resolution and level of detail.

While none of these techniques provides a direct validation of the model, each of these techniques provides insight into the sensitivity of the model predictions to key assumptions regarding the analysis. The response of the predictions to these procedures can be evaluated with respect to prior expectations, comparison with analogous systems, and theoretical justifications.

16.3 Comparison with epidemiological data

To make a valid comparison with a foodborne pathogen risk estimate, at least three factors need to be considered when deriving an epidemiological estimate from human surveillance data (Powell, Ebel and Schlosser, 2001). These factors are (i) Cluster-weighted rate of illness; (ii) Adjustment of surveillance data to account for under-reporting; and (iii) Etiological fraction attributable to food products. These three factors are discussed in more detail below.

If the risk assessment estimates the incidence of illness at the national level, the epidemiological estimate will need to extrapolate the rate of illness beyond the surveillance area to permit comparison at the national level. In this case, the raw reported rate in each surveillance area may be weighted by the population of the region represented by the area (e.g. state population size) to obtain a weighted average rate of illness (e.g. cases per 100,000 in the national population). If multiple years of surveillance data are available, then the data can be used to characterize year-to-year variability in the rate of illness.

Estimating the actual incidence of illness requires adjustment for recognized sources of underreporting in human surveillance data (Scallan *et al.*, 2011; Williams, Ebel and Vose, 2011b). For example, some ill persons do not seek medical care, physicians do not obtain stool specimens from all patients, laboratories do not culture all stool samples for the pathogen of concern, and some proportion of the lab results are false negatives. If estimates are available on the proportion of cases at each step in the reporting process, the negative binomial distribution can be used in sequential fashion to estimate the number of cases missed at each step. In some cases, the proportions may be dependent on the nature or severity of symptoms. For example, a person with bloody diarrhoea may be more likely to seek medical care than one with non-bloody diarrhoea. In this case, the proportion of cases with different levels of symptoms must be estimated prior to accounting for the number of cases missed at each step, and the adjusted symptom-specific estimates are summed to estimate the total number of cases (Hall *et al.*, 2008). In general, the degree of under-reporting tends to be substantial (WHO, 2015), and varies among countries and between regions within countries (Scallan *et al.*, 2011).

The etiological fraction refers to the proportion of cases attributable to an exposure pathway or a specific food product (Greig and Ravel, 2009; Mullner *et al.*, 2009; Painter *et al.*, 2013; Pires, 2013; Pires *et al.*, 2009). If the scope of the risk assessment is limited to a particular food product, then the proportion of cases due to other exposure pathways (e.g. other foods, drinking water) needs to be subtracted from the overall estimate of illness obtained from the human surveillance data. In general, empirical data on the etiological fraction are scarce. It may be possible, however, to specify a range of uncertainty on the basis of expert judgement (e.g. Vally *et al.*, 2014).

16.4 Extrapolation and robustness

Model robustness refers to the performance of the model when its assumptions are violated. In this context, assumptions include model form and model inputs. Extrapolating model results to other settings may involve many forms of extrapolation (e.g. from the present to the future, from one

geographical region to another, from one microorganism to another, from animals to humans, from clinical trial subjects to the general population, from one population to another, from available data to values beyond the observed range , from experimental settings to operational environments). Some extrapolations can be made with relative confidence, while others can not. Some degree of extrapolation may be inevitable, since the demands of risk management may outstrip the supply of relevant science. The importance of various forms of extrapolation made in risk assessment needs to be considered and, to the extent feasible and relevant to the decision at hand, characterized in a clear manner, either quantitatively or qualitatively.

Extrapolation is explicit when the selected values of model inputs are outside the range of values used to calibrate or validate the model, or both. However, there can also be hidden extrapolation. A hidden extrapolation occurs for a combination of values of two or more model inputs such that these values individually are enclosed by ranges used for calibration and validation, but for which the specific combination was not included or approximated during calibration or validation. Thus, simple range checks on each input will not guarantee that a hidden extrapolation cannot occur. Hidden extrapolation would typically be more of a problem for a system in which there are highly sensitive interactions among inputs or when model inputs are highly correlated.

A model that is calibrated to a narrow range of values for each input may not be robust when applied to sensitivity or uncertainty analysis. The use of ranges or distributions, rather than point estimates, could lead to hidden or explicit extrapolations of the model. Situations may also arise in which some iteration of Monte Carlo simulation give division by zero or unbounded result errors. Such problems can often be solved by investigating model assumptions, checking model inputs, or adding error trapping in the software. Problems such as these can arise in practice, particularly when working with a model or computer code that someone else developed and for which documentation may be inadequate.

A model is considered to be robust if it responds in a reasonable manner to variation in input values, while at the same time not being easily subject to singularity points or other structural issues that lead to substantial magnification of errors in input values, whether because of uncertainty or user error. A model that is based on sound theory might be used with more confidence compared with a purely empirical model that is essentially “curve fitting”.

16.5 Credibility of the risk assessment

Documentation, validation, and review are necessary criteria for the credibility of a risk assessment. None of these criteria is sufficient by itself, however, as credibility depends on all three criteria being satisfied in a manner that is proportionate to the stakes of the decision. Documentation and scientific review are discussed below and validation has already been discussed in Section 16.2.3.

16.5.1 *Risk assessment documentation*

Risk assessment documentation should serve both technical and non-technical readers. One way to address this need is to provide a technical document with all modelling details and a less technical interpretive summary.

Risk assessment documentation must enable the analysis to be independently reproduced. Modern programming tools, free and open-source software, and sharing of risk assessment model code may assist in this aim. The principle of transparency also requires that the source or basis for model inputs and assumptions be clearly stated, e.g. by references to scientific literature, evaluation criteria or expert judgement. The expectation for risk assessment documentation should be reasonable, however, because in some cases, assumptions may be based on common knowledge or

generally accepted practices in the field. For example, the log-normal distribution is commonly assumed for modelling variables that are the product of several other variables. Because risk assessments are difficult to fully validate, and because such assessments are used to inform public health decision-making at various levels, including local, national, and international, it is critically important that the information used for the assessment, including the model, be accessible for review by experts and the lay public (e.g. FAO/WHO, 2009c, 2009d).

The information in the documentation of a risk assessment should include:

1. Data or references to data sources;
2. Scenarios, including the temporal and spatial aspects of the exposure scenarios, the specific hazards addressed, the specified pathogens included, exposed populations and exposure pathways;
3. The analytical model used for analysis, including the theoretical or empirical basis;
4. Discussion and comparison of alternative model formulations, and justification for choices made regarding model structure;
5. Assumptions regarding values assigned to model inputs, including point-estimates, ranges and distributions;
6. Model verification, including assessment of results from sensitivity and uncertainty analysis;
7. Model anchoring (calibration);
8. Model validation; and
9. Computer implementation of the analytical model, including software design.
10. An interpretive summary that is understandable by the risk manager.

16.5.2 *Scientific peer review*

The credibility of risk assessment results can be improved by the process used to develop the results. Peer and public review of risk assessment results are an essential part of the process, but each type of review generates distinct and sometimes conflicting demands that should be addressed on their own terms.

Morgan and Henrion (1992) identify exposure to peer review as a basic tenet of good policy analysis. The focus of a scientific peer review is highly dependent on the risk management question that the risk assessment is intended to inform. Without reference to a well-defined and specific risk management question, peer review of a risk assessment may fail to focus on the particular uncertainties that are most likely to influence the risk management decision. For example, if the risk management question is "What is the likelihood that a specific pathogen occurs in a particular food production process?" then data gaps and other uncertainties regarding post-production processes are irrelevant to the decision. Peer review comments regarding the scope of the risk assessment, while potentially useful for future risk assessments, are not relevant to the adequacy of the risk assessment under review to inform the risk management decision for which it was intended. If a risk assessment has multiple objectives, peer review may help to identify which objectives an assessment satisfies, since an assessment that is adequate to inform one decision may be insufficient to support another. A thorough review can be difficult and time consuming for a complex risk assessment, even if the documentation is adequate. In the case of large, complex risk assessments, a thorough review may require a multidisciplinary team and a significant budget, e.g. the NAS review (NAS, 2002) of the FSIS risk assessment of *E. coli* O157 in ground beef (FSIS, 2001). The substantive and procedural benefits of peer review should therefore be balanced by time and resource considerations. The level and extent of review should be proportionate to the stakes of the decision, taking into consideration the need for immediate action in the event of actual public health emergencies.

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