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TOOLS FOR MICROBIOLOGICAL RISK ASSESSMENT

REPORT

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TOOLS FOR MICROBIOLOGICAL RISK ASSESSMENT

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1. GENERAL OVERVIEW

*T*he microbiological safety of food is of fundamental importance to all those companies and government organisations involved in the production, processing, distribution, retail and regulation of foods and drinks. Although quality, portion size, packaging format and other such issues are open to choice and commercial decisions, issues associated with the control of safety and pathogenic microorganisms are essentially "non-negotiable". While there are many factors that impact on food safety, current trends are providing new challenges for food safety managers, including:

- Increasing demand for convenience

- Demand for fresher, healthier and less processed foods

- New developments in food processing and packaging

- International sourcing of ingredients and products

There have also been significant developments in the approach to the microbiological safety control measures applied to food. The ILSI Europe keynote document entitled "Food Safety Management Tools" (Jouve *et al.*, 1998) succinctly describes the approaches current at that time to ensure safe food. Essentially, these measures were based on Good Manufacturing Practice (GMP) and Good Hygienic Practice (GHP) and on the implementation of a thorough Hazard Analysis Critical Control Point (HACCP) system. Although these tools are equally important today, a range of other objective control measures and risk assessment procedures are steadily being adapted to varying degrees by both government and industry. This is reflected in the recently updated version of the "Food Safety Management Tools" document (Crossley and Motarjemi, 2011), which now includes more information on the role of microbiological risk assessment (MRA). This publication provides a more in-depth review of the tools available to support the application of MRA.

MRA has emerged as a comprehensive and systematic approach for addressing the risk of pathogens in specific foods and/or processes. From a governmental point of view, the Agreement on the Application of Sanitary and Phytosanitary Measures (SPS) and the General Agreement on Tariffs and Trade (GATT) can especially be considered to have given a boost to the development of MRA, while on the other hand the fast development of quantitative microbiology since the 1980s has been a fertile basis for MRA development. Whilst the formalised structure of an MRA is well known, and is generally seen as particularly appropriate to government health agency decision-making tasks, it also has relevance to a number of industrial situations such as shelf-life determination, thermal process setting, ingredient selection, assessment of innovative non-thermal processes and new product development. The industrial application of MRA has been reported by the Campden BRI (CCFRA, 2003,2004, 2007). The document provides an extensive description of the different elements of the structured risk assessment process, which can be utilised by industry to aid the understanding of safe food production.

The focus of this report is to aid the food safety manager by providing a concise summary of the tools available for the MRA of food. After an introduction to MRA in Section 2, the importance of data is considered in Section 3. Next, Section 4 describes the different types of models, including models for recontamination, and, importantly, how and when to use them. Software tools currently available to aid the risk assessment process are described in Section 5, including both those freely available on the internet and others available commercially. A critical final section addresses the interpretation of results from MRAs and the outputs from the use of the various tools.

2. MICROBIOLOGICAL RISK ASSESSMENT

2.1 Introduction to risk assessment

Risk assessment for food safety sits within the framework of "risk analysis", provided by the Codex Alimentarius Commission (Codex), which also includes "risk management" and "risk communication" as interdependent concepts.

Risk assessment takes place within a risk management context, to aid decision-making on managing a microbiological hazard, and considers knowledge on the nature of the hazard and the likelihood of exposure to that hazard. The assessment of microbiological risk can vary from a single expert judgement to a more comprehensive qualitative and quantitative risk assessment procedure based on the principles described by Codex in its "Principles and Guidelines for the Conduct of Risk Assessment" (CAC, 1999). The Codex document lists steps in the risk assessment process: statement of purpose, hazard identification, hazard characterisation, exposure assessment, risk characterisation, documentation and re-assessment. The core elements of hazard identification, hazard characterisation, exposure assessment and risk characterisation are described in Section 2.2.

In a more recent Codex guidance, the concept of a "risk profile" has been adopted under the Codex risk analysis approach as part of the "preliminary risk management activities" and is "a description of the food safety problem and its context" (CAC, 2007). A risk profile may be considered a structured "narrative" type of evaluation, or a "preliminary risk assessment". In addition to scientific information, other considerations such as public perceptions, trade impacts and management/intervention options may also be included in the document (Lammerding, 2007). Another relatively recent development has been the introduction of the concept of a "Food Safety Objective" (FSO) criterion to link food risk assessment to risk management (ICMSF, 2002); the interaction of FSOs with MRA was considered at an ILSI Workshop in Marseille, France and the discussions published (Stringer, 2004, 2005).

The information generated through conducting a risk assessment, such as a risk estimate, ranking of risks, identification of key controlling or risk-generating factors, or highlighting of data gaps, can assist governments in their role of setting national policies, criteria or providing public health advice, and also assist industry in their ambition to design innovative yet safe foods for consumers.

2.2 Risk assessment elements

The core elements of an MRA, i.e. hazard identification, hazard characterisation, exposure assessment and risk characterisation, are outlined in more detail below.

2.2.1 Hazard identification

Hazard identification is the first step in risk assessment. Hazard identification is defined in the Codex "Procedural Manual, Fourteenth Edition" (CAC, 2004) 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". It is a qualitative process and, in addition to selecting an organism (or organisms) of concern, serves to document the important information known about the pathogen, food product and host interface (Lammerding *et al.*, 2001).

Hazards can be identified from publically available information such as published literature, epidemiological studies, foodborne disease reports, etc. In the description of the hazard, the hazard identification step will usually also summarise other aspects, such as the types of disease caused (e.g. acute or chronic) and the susceptible populations; and the mode with which the organism effects the host (e.g. through the action of toxins or through infectious mechanisms).

2.2.2 Hazard characterisation

Hazard characterisation is defined in the Codex "Procedural Manual, Fourteenth Edition" (CAC, 2004) 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. For chemical agents a dose–response assessment should be performed. For biological or physical agents a dose–response assessment should be performed if the data are obtainable".

In MRA, this step provides a qualitative or quantitative description of the severity and duration of adverse effects that may result from the ingestion of a microorganism or its toxin in food. When establishing a dose–response relationship the different end points, such as infection or illness, should be taken into consideration (CAC, 1999).

Mathematical modelling of the dose-response relationship is recognised as a useful adjunct to the descriptive analysis of clinical or epidemiological information or data relating to foodborne illness. A microbiological dose-response model describes the probability of a specified response from exposure to a specific pathogen (or its toxins) in a specified population as a function of the ingested dose. The biological basis for microbiological dose–response models derives from major steps in the disease process: exposure, infection, illness and consequences (recovery, sequelae or death). The issue of response derives from the interactions between the pathogen, the host and the food matrix.

Current thinking is that a single viable infectious pathogenic organism is able to induce infection (the "single-hit concept") (FAO/WHO, 2003). Mathematically, there is always a non-zero probability of infection or illness when a host is exposed to an infectious pathogenic organism. This non-threshold model is a more cautious and more appropriate approach than is the threshold model, which uses a minimum infectious dose (MID) to measure the infectivity of an organism. MID is an expression of the lowest number of organisms required to initiate an infection in any individual under given circumstances. Therefore, it is believed that prudent public health protection requires the application of non-threshold approaches to the assessment of microbial dose-response relationships.

A dose–response model gives the probability of illness according to the amount of ingested pathogenic microorganisms. Among d ingested microorganisms, some might survive human host barriers and subsequently initiate infection and cause illness. Illness probability is defined as the probability of achieving this sequence of events. If each ingested microorganism has the same probability to provoke illness, r, then the number of microorganisms surviving different barriers follows a binomial distribution. If each microorganism is capable of inducing illness, then the probability of illness (P_{ill}) given d ingested microorganisms is the complement of the probability of absence of illness:

$$P_{ill}(d,r) = 1 - (1-r)^d$$

The underlying assumption of the single-hit model is then the absence of interaction between microorganisms, where r is assumed identical for all microorganisms in the ingested dose, independent of the size of the dose, the state of the microorganisms, the host and previous exposure to the pathogen. Starting from this basic function, 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 r. Not much information on dose–response models for toxins is currently available .

2.2.3 Exposure assessment

Exposure assessment is defined in the Codex "Procedural Manual, Fourteenth Edition" (CAC, 2004) 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".

Exposure assessment in MRA includes an assessment of the extent of actual or anticipated human exposure to microbiological pathogens or microbiological toxins, i.e. an estimate of the likelihood of their occurrence in foods at the time of consumption and their level, within various levels of uncertainty (CAC, 1999). Qualitatively, foods can be categorised according to the likelihood that the foodstuff will or will not be contaminated. Predictive microbiology models can be useful to assess the growth, survival or death (or time to toxin production) of microorganisms as a function of the food and environmental conditions encountered from raw materials to the food consumed, and are particularly important when making quantitative estimates.

2.2.4 Risk characterisation

Risk characterisation is defined in the Codex "Procedural Manual, Fourteenth Edition" (CAC, 2004) as "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 characterisation and exposure assessment".

Risk characterisation brings together all of the qualitative or quantitative information of the previous steps to provide a soundly based estimate of risk for a given population.

2.3 Risk assessment types

Risk assessments can be broadly classified as qualitative or quantitative (Figure 1).

Figure 1: Overview of types of risk assessment. From top to bottom, the risk assessments become more complex and data-demanding, but also more informative.

Risk assessment
      systemic, logical, decision support
  Qualitative
      non numerical description of likelihood
  Quantative
      numerical
    Deterministic
      point estimates, does not include randomness
    Stochastic
      uses probability distributions to characterise randomness, variability and uncertainty
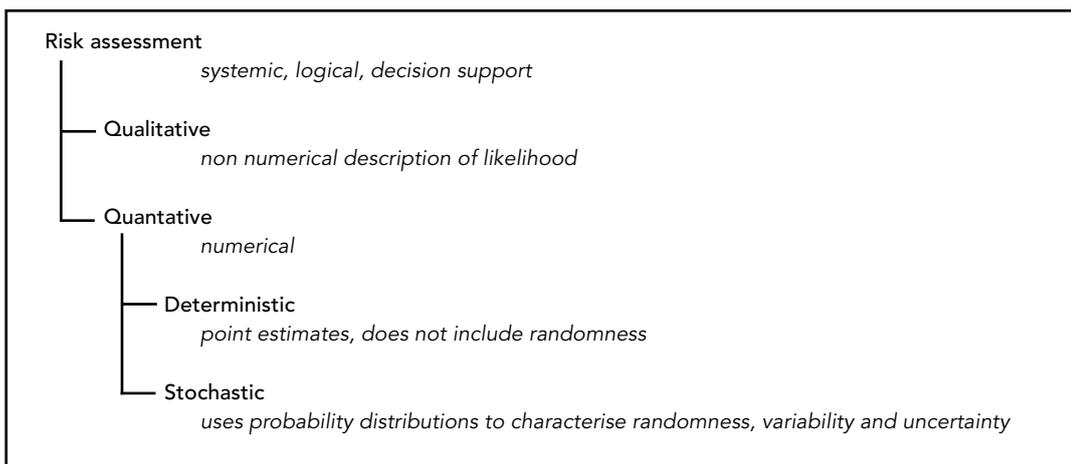
2.3.1 Qualitative risk assessment

Qualitative risk assessments involve the descriptive treatment of information in order to estimate the magnitude of risk and the impact of factors affecting risk, whereas quantitative assessments work with numerical data (Fazil, 2005). However, in reality, there are no sharp lines defining these categories as they represent a progression of increasing quantification and analytical sophistication. Qualitative risk assessments still require the use of quantitative data and analyses, and are sometimes

described (although inappropriately) as "semi-quantitative" (Lammerding, 2007). Following the framework for MRA laid out by Codex, qualitative risk assessments should be more than just a literature review on the problem in hand and represent a systematic and logical approach that should arrive at a robust estimate of the risk being considered, albeit a non-numerical one. These estimates are necessarily descriptive characterisations of likelihood and impact (such as negligible, low, medium or high), which should be clearly defined to avoid misinterpretation (Fazil, 2005), and can allow the ranking of different risks.

A qualitative MRA might be established before a quantitative assessment to give some idea of potential magnitude of risk, and to indicate whether or not a more detailed analysis is needed to better understand the issue (Lammerding, 2007), e.g. as part of a risk profile. Qualitative MRAs may be undertaken prior to the availability of key data to help direct the collection of those data. Progressing to a more quantitative approach increases the flexibility, acceptability, objectivity and power of the decisions made (Fazil, 2005). Correspondingly, there is typically an increase in the requirements for data, degree of detail in describing the system of concern, analytical expertise and time involved when utilising increasingly sophisticated methods of analysis (Lammerding, 2007).

2.3.2 Quantitative risk assessment

Quantitative microbiological risk assessments (QMRA) can use deterministic or stochastic models. Deterministic and stochastic models can be differentiated along the lines of their treatment of randomness and probability (Fazil, 2005). Deterministic models, although they can include probabilities, do not include any form of randomness or stochasticity as described by probability distributions in their characterisation of a system. In a deterministic model, regardless of its complexity, the outputs are determined once the inputs have been defined. Conversely, stochastic models include components of randomness within their definition. Stochastic models tend to be a better representation of natural systems, given the randomness inherent in nature itself.

Deterministic models will tend to use single-point estimate values, and stochastic models use ranges or statistical distributions of values as inputs. For deterministic assessments, all variables are assigned a certain fixed value, which may represent a mean value or a maximum or "worst-case-scenario" of a variable data set for example. The calculations result in a single number (which may include confidence intervals) as the risk estimate outcome. Once the relationships between the factors in a model are determined, deterministic models are relatively simple to calculate. However, even with consideration of confidence intervals, these do not provide much insight into how likely (or unlikely) it is that the adverse event will occur, nor give useful insights about the drivers of the risk (Lammerding, 2007). An assessment using worst-case inputs gives an extreme output, without regard for the low likelihood that such an extreme will occur, whereas an assessment using mean values will arrive at an "average" risk but then ignore extremes that may be important (e.g. in representing a susceptible subpopulation) or infrequent but with severe consequences (Fazil, 2005). The outputs from deterministic risk assessments may be more useful when used as an indicator of relative risk, which can provide focus for risk management activities without the need for more precise risk estimates.

The stochastic approach constructs risk assessments that incorporate the variability inherent in the system itself as well as the uncertainty in the input parameters. The statistical distribution of the variables (the shape of the distribution curve and its parameters) is required, and combining the distributions requires more expertise than for single numbers in an equation to calculate outputs. By using simulation software based on techniques such as Monte Carlo analysis, the effect of variability on intermediate results and the final outcome can be calculated. For every simulation (i.e. literally, to simulate what may occur in reality) a random value of each variable is selected, resulting finally in a probability distribution of the risk under consideration (Lammerding, 2007). Software tools to conduct stochastic risk assessments are considered in Section 5.

3. DATA FOR MICROBIOLOGICAL RISK ASSESSMENT

*M*RAs are based on quantitative models, but also require quantitative data. So in addition to the structure of the models, the hypotheses made and the methods and tools used, the quality of the results of an MRA depends largely on the availability of appropriate data (Figure 2). These data are from very different domains and include biological data (organisms), food data, process data and consumer data (e.g. handling practices, frequency and quantity of servings).

Figure 2: Risk assessments are founded on the solidity of the underlying data and the underlying models.

Microbiological risk assessment		
Data organism food process consumer		**Model** structure hypothesis methods tools
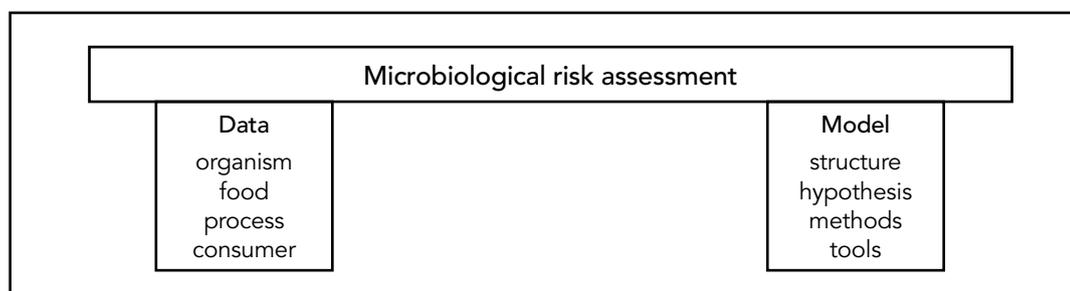
For an MRA, there is a need for a multitude of data on very different aspects: the food product, the production chain, consumer habits, organism characteristics, ecology, human susceptibility and strain virulence. For a robust risk assessment, in addition to good estimates, the variability and uncertainty in the data needs to be clearly reported as well as the data that are excluded, with reasoning (FAO/WHO, 2008).

Certain estimates will have large variabilities, for example storage time (for certain foods), heat inactivation parameters and virulence of strains. Furthermore, in certain cases variabilities are correlated, e.g. organism characteristics. The value of the minimum temperature of growth is likely to be related to the heat inactivation characteristics of an organism, and the refrigerator temperature might be correlated to the storage time, both positively correlated (abuse behaviour) as well as negatively correlated (due to effects of spoilage). The existence of such correlations needs to be investigated and, if possible, evaluated and quantified, because they can have a large impact on the risk estimate.

Additionally, data should always be evaluated for their representativeness for the situation under study, and a lack of exact representativeness will result in uncertainty. Also, in certain cases different estimates exist, all being realistic but coming from different sources, meaning that uncertainty exists in the real value of a factor. Uncertainty is often even more difficult to quantify than variability.

Finally, it is important to have a good description of the data sources (transparency), including a discussion of the factors and decisions mentioned above. Assumptions have to be made, but these and their potential impact need to be discussed and made explicit.

Data gaps can be identified and evaluated at the start of the process, but even more importantly at the end of the analysis, when one needs to investigate which data gaps are most relevant concerning the uncertainty in the outcome. This aids risk managers in deciding where additional research for a more precise risk estimate is desirable.

3.1 Key data for hazard identification

As indicated by Codex (CAC, 1999), information on hazards can be obtained from the scientific literature, databases such as those in the food industry, government agencies and relevant international organisations, and through consultation with experts. Relevant information includes data from areas such as clinical and epidemiological studies, surveillance and outbreak investigations, investigations of the presence and characteristics of microorganisms throughout the food chain from primary production up to and including consumption and studies on analogous microorganisms and situations.

3.2 Key data for hazard characterisation

Existing quantitative dose–response data may be obtained from the literature (see for example FAO/WHO, 2003) or public health databases that include data from outbreak investigations and from clinical studies on humans or laboratory animals. Published risk assessments and books (e.g. Haas *et al.*, 1999) on the subject can also be a valuable source of dose–response information.

There are several important factors that need to be considered with data for hazard characterisation. These are related to the microorganisms, the food product and the human host. In relation to the microorganism the following are important: the capability of the microorganisms to replicate; any change in virulence and infectivity of microorganisms due to their interaction with the host and the environment; evidence of transfer of genetic material between microorganisms that might lead to the transfer of characteristics such as antibiotic resistance and virulence factors; the spread of microorganisms through secondary and tertiary infection; any delay in the onset of clinical symptoms following exposure; and persistence of microorganisms in certain individuals leading to continued excretion and potential spread of infection. Low doses of some microorganisms can in some cases cause infections and finally result in a severe effect. The attributes of a food may alter the microbial pathogenicity, e.g. high fat content of a food vehicle, or components that can buffer the pH of the stomach.

In relation to the host, the following may be important: genetic factors such as Human Leucocyte Antigen (HLA) type; increased susceptibility due to breakdown of physiological barriers; individual host susceptibility characteristics such as age, pregnancy, nutrition, health and medication status, concurrent infections, immune status and previous exposure history; population characteristics such as population immunity, access to and use of medical care and persistence of the organism in the population.

Although the importance of organism, food and host factors is generally acknowledged, no quantitative risk assessment has to date been able to incorporate them all, due to a lack of appropriate quantitative data, the difficulties in generating new scientific data in this field and a lack of suitable models to integrate them.

In the absence of a known dose–response relationship, risk assessment tools such as expert elicitations could be used to consider various factors, such as infectivity, which is necessary to describe hazard characterisation. Additionally, experts may be able to devise ranking systems so that they can be used to characterise the severity and/or duration of disease.

3.3 Key data for exposure assessment

Factors that must be considered for exposure assessment include the frequency of contamination of foods by the pathogenic agent and its level in those foods over time. For example, these factors are influenced by the characteristics of the pathogenic agent; the microbiological ecology of the food; the initial contamination of the raw material (including regional and seasonal variability); the level of sanitation and process controls; and the methods of processing, packaging, distribution and storage of the foods, as well as any preparation steps such as cooking and holding. The presence, growth, survival or death of microorganisms, including pathogens in foods, are influenced by processing factors and extrinsic factors (like the storage environment, including the temperature of storage, the relative humidity of the environment and the gaseous composition of the atmosphere), intrinsic factors (e.g. pH, moisture content or water activity, nutrient content, the presence of antimicrobial substances), and implicit factors (like competing microflora). Predictive microbiology can be a useful tool in an exposure assessment (see Section 4). Another factor that must be considered in the assessment is patterns of consumption that impact upon the serving size and frequency of consumption. This relates to socio-economic and cultural backgrounds, ethnicity, seasonality, age differences (population demographics), regional differences and consumer preferences and behaviour. Other factors to be considered include behavioural factors, like the role of the food handler as a source of contamination, and abusive environmental temperatures.

Contamination can occur from the raw materials, the environment (recontamination) or from other product units (cross-contamination). These contamination levels are determined by the frequency of contamination, the concentration and the transfer rate. For example, a global analysis was carried out of a large dataset of air contamination data and resulted in a method for estimating concentrations and transfer in specific conditions (den Aantrekker *et al.*, 2003a). Generally, (re)contamination data are difficult to obtain. Often, pertinent data needed for the analysis are lacking, or available only with great uncertainties, due to lack of representativeness of the specific data used for the application under study.

3.4 Sources of data

3.4.1 Models
In order to quantify growth and inactivation of microorganisms, quantitative models (see Section 4), or parameters from quantitative models can be used. Examples of tools are given in Section 5.

3.4.2 Scientific literature including quantitative risk assessments
Many specific data can be found in the scientific literature, in databases (e.g. ComBase, public health databases and many others) and in quantitative risk assessments (QRAs) (both in the scientific literature and as reports from governments or international organisations). For example, virulence data of specific organisms can be used from a QRA for another commodity, and variability in refrigerator temperatures can be obtained from other QRAs.

3.4.3 Experiments and surveys
For specific food products, challenge or storage tests can be carried out to validate model predictions or to obtain product-specific data. Furthermore, surveys can be carried out on serving sizes and frequency of consumption. These data can also be derived from market volumes, either from industry or commodity boards.

3.4.4 Expert opinion

In the absence of suitable observational or experimental data, parameter estimates required for risk assessment can be obtained using expert judgement. This is based on the assumption that specific subject experts will have better, more objective knowledge of the features for which data are lacking than risk assessors or risk managers. Generally, multiple experts need to be questioned and both best estimates and the variability and uncertainty need to be addressed. Use of expert opinion occurs frequently in risk assessment, and advanced methods for expert elicitation are available, including validation and weighing of expert opinion (Cooke, 1991; Cooke and Gossens, 2000; Van der Fels-Klerx *et al.*, 2005).

3.4.5 Combination of data sources

In general it is best to use at least two of the above mentioned data sources, since in many cases obtaining data from only one source might not be representative. Model predictions validated with a challenge test, or serving frequencies corroborated with market data, give much more confidence in the solidity of the data used than the use of one data-source only, decreasing uncertainty in the final risk estimate.

4. MODELS FOR MICROBIOLOGICAL RISK ASSESSMENT

Quantitative microbiological risk assessment (QMRA) requires mathematical models and supporting data to describe the dynamics of changes in the levels of microbial contamination of foods during food production and processing, and the consequences for human health. It therefore builds on several types of models. First of all, the risk assessment will require input in terms of prevalence and concentration of the microbial hazard in the food concerned. Next, various processes will affect the prevalence and concentration by the mechanisms of bacterial growth and inactivation, recontamination and mixing and partitioning of food products (Nauta, 2008; Bassett, 2010). Finally, dose–response models describe the effect of exposure in terms of human illness.

4.1 Models for hazard identification

4.1.1 Decision support models
By combining databases and qualitative reasoning, structured methods of hazard identification can be set up. Data from epidemiological studies or source attribution could be used for this. The advantage of following such a systematic approach is that the same (traceable) response is given if the same question is asked (not depending on place, time or person) and that such a system can be updated if new information becomes available. Examples of such systems for the identification of hazards were described by Zwietering *et al.* (1992) and van Gerwen *et al.* (1997). These systems are based on a coupling of databases containing parameters of organisms and food products (pattern matching), in combination with well-defined qualitative knowledge rules.

4.1.2 Risk ranking models
For the selection of the relevant hazards, risk ranking models can also be used (for example see Risk Ranger, described in Section 5) in which the relative risk is calculated for different product, pathogen and processing combinations. This can aid prioritisation of hazard/product combinations for conducting a more in-depth QMRA.

4.2 Models for exposure assessment

4.2.1 Statistical models of prevalence and concentration
Statistical models to describe prevalence and concentration distribution from empirical data are described in an ILSI Europe Report "Impact of Microbial Distributions on Food Safety" (Bassett, 2010). The sampling methods and the quality of the analytical methods (e.g. sensitivity, specificity, reproducibility) need to be considered, in addition to the statistical aspects to describe these data. Censored data are often found (due to a limit of detection, for example < 1 in 25 g), particularly for pathogens. These censored data can be the result of either real prevalence (real absence or presence) or low concentration and detection probability. These aspects need to be considered when using data to evaluate the impact for the specific analysis carried out, for example by estimating the prevalence in a whole product unit based on censored prevalences in 25 g, making use of statistical techniques.

4.2.2 Models of growth
4.2.2.1 Primary models
Models describing the development of numbers of organisms as a function of time (both for growth or inactivation) are called primary models. The microbial growth curve (as log numbers) typically has a characteristic sigmoid nature, with an apparent slow phase followed by a more rapid increase followed

by a slowing down, finally reaching a maximum population level. A variety of models can be used to fit the curve, such as the logistic, Gompertz, Richards, Schnute and Stannard model (Zwietering *et al.*, 1990); the Baranyi model (Baranyi *et al.*, 1993; Baranyi and Roberts, 1994); and the three-phase linear (Buchanan *et al.*, 1997) models. The effectiveness of the chosen model is dependent not only on the ability of the model to reflect the observations but also on the purpose of modelling and the quality and type of data provided.

4.2.2.2 Secondary models

Primary models provide data on lag time, maximum growth rate and the maximum population reached from a given initial inoculum. As conditions change, these values change and secondary models attempt to produce mathematical formulae describing these changes, e.g. the effect of temperature on the lag time or the effect of pH on the specific growth rate. The aim of such modelling is to produce a model with the fewest parameters (parsimony), which describes the observed growth parameters so that predictions can be made (Ratkowsky, 1990). The main factors studied for their effects on growth in the primary models available are:

Temperature

Of all the hurdles to microbial growth in a foodstuff, temperature is one of the most critical. Ratkowsky *et al.* (1982) found that a square root expression fitted the observations of growth rate at temperatures below the maximum growth temperature. A distinct set of temperature models have been developed that are empirical in nature but that use the cardinal temperature values to provide a good fit to observed data having interpretable parameters (Rosso *et al.*, 1993), with cardinal parameters the minimum, maximum and optimum values for growth.

Acidity

For the effect of pH, exponential or square root models were initially developed, followed by Cardinal models (Rosso *et al.*, 1995).

Water activity

McMeekin *et al.* (1987) showed that there was a linear relationship between water activity (a_w) and the maximum specific growth rate. Rosso and Robinson (2001) built on the success of the cardinal parameter models described previously by constructing a general model for the effect of water activity.

Preservatives (weak acid and similar additives)

There is a vast range of known antimicrobial compounds but only a narrow range that can be used in food. The latter are confined, mainly, to the weak acids such as lactic, acetic, propionic, benzoic and sorbic acid. Current modelling has focussed on these weak acids, particularly lactic acid, and the antimicrobial action of nitrite. The effect of natural antimicrobials such as those found in essential oils and spices and the use of antimicrobial peptides such as nisin have also been examined but are less often modelled.

Redox and atmosphere

There are no fundamental models describing the effect of redox on growth. However, given the feasibility of the Cardinal models it could be suggested that such a model could be of general applicability. The relationship between the partial pressure of oxygen (pO_2) and redox potential (E_h) depends on the chemical nature of a culture medium or food, and knowledge of both is required in order to assess the probable influence of these parameters on growth. Carbon dioxide is the gas of choice for modified atmosphere packing (MAP) and was first shown by Pasteur in 1877 to kill *Bacillus anthracis*. An example of predictive models for the effect of CO_2 can be found in Dalgaard (1995).

Combined effects

For most foods, a combination of the principal environmental factors (temperature, a_w, pH, atmosphere and antimicrobials) prevents or slows down microbial growth. There are two main methods for the quantitative study of combined hurdles: (1) through models describing the combined effect of individual factors, and (2) through modelling composite factors using response surfaces.

The Gamma hypothesis (Zwietering *et al.*, 1996) states that inhibitory processes affect microbial growth independently and that they combine together in a multiplicative manner, except where synergy or antagonism between factors occurs. Furthermore, the Gamma concept suggests that by understanding the effect of individual factors, each for example described by a Cardinal model, they can be combined in the form of "Gamma factors" or ratios of the observed growth to the uninhibited growth.

Surface response models describe variables by multiple regressions. These have the advantage of being easy to produce, but lack any mechanistic insight. One peculiarity of surface response models is that the cross-terms of the polynomial functions are often used to suggest the presence of interactions between the parameters, e.g. terms signifying interactions between temperature and salt concentration or between temperature and nitrite levels. Indeed, this is one of the problems with such models – they are purely empirical fitting functions with no mechanistic justification, yet cross-terms are often considered to show interactive effects. Hence, the polynomial models are at odds with the Gamma hypothesis. Additionally, these models provide deterministic information with no or little indication of variability or uncertainty.

There are many examples in which the temperature and pH Cardinal models are used in conjunction with other Gamma models to describe observations of growth. The Cardinal models are relatively easy to apply and the data required to produce a Cardinal model are often available in the open literature.

Despite the increased number of data and models for the growth rate and the lag time for different bacterial pathogens, the quantitative data on the effect of the food environment on the maximum population density of the pathogen is limited. In some foods, growth of bacteria such *Listeria monocytogenes* might be rapid initially but ends after a short growth period because of limitation in some nutrients, or competition from some specific microbial flora (Dalgaard and Jorgensen, 1998), which was termed the Jameson effect (Jameson, 1962; Ross *et al.*, 2000). Efforts on evaluating the Jameson effect and expressing it in quantitative terms (i.e. using mathematical models) could significantly increase the accuracy of risk assessments (Coleman *et al.*, 2003; Pouillot *et al.*, 2007), although these effects will only be relevant in specific cases where pathogens and other organisms can reach levels close to the maximum population density.

Another important data gap is the integration of natural variation between bacterial strains into the predictive models. In certain cases, available models are based on growth data of a single strain. However, several studies have reported that growth kinetics of pathogens can vary significantly between different strains, e.g. *L. monocytogenes* (Begot *et al.*, 1997; Lianou and Sofos, 2007), *Escherichia coli* O157:H7 (Whiting and Golden, 2002) and *Staphylococcus aureus* (Lindqvist, 2006).

Most available models are developed in laboratory media and include the effect of certain environmental factors on microbial growth, and some have been validated by experiments on foods. In foods, however, microbial growth can be affected by other factors that are not included in the models, such as the physiological state of the cells, the food structure, the microbial interactions or the presence of antimicrobial compounds. In general, it has been observed that growth in foods is slower than growth predicted by models developed in broth media. The models described provide deterministic information with no or little indication of variability or uncertainty.

4.2.3 Models of inactivation
4.2.3.1 Primary models
Models describing the inactivation or survival of pathogens in foods have been used since the 1920s, when they were applied to *Clostridium botulinum* spores in low-acid canned foods (McKellar and Lu, 2004a). The assumption has generally been made that inactivation follows simple first-order reaction kinetics under isothermal conditions (i.e. the number of surviving cells decreases exponentially, or log-linearly), which has given rise to the use of the *D*-value (time required for a 1-log reduction in population), available in published literature for a wide range of microorganisms.

Non-linear survival curves have, however, been reported for many years (Moats *et al.*, 1971, cited in McKellar and Lu, 2004b), displaying "shoulders" or lag prior to inactivation and/or "tails" following the linear phase. Modelling inactivation curves with shoulders or tails has been performed using two-phase linear models as developed by Whiting (Whiting, 1993, cited in McKellar and Lu, 2004b); non-linear approaches, e.g. the exponentially damped polynomial model for a concave curve (Daughtry, 1997, cited in McKellar and Lu, 2004b); the Fermi equation (mirror image of the logistic function) for symmetrical sigmoidal decay curves (Pruitt, 1993, cited in McKellar and Lu, 2004b), and variations thereof; or other mirror images of growth functions such as the Baranyi model (Koutsoumanis, 1999, cited in McKellar and Lu, 2004b) and a reparameterised Gompertz function (Linton, 1995 cited in McKellar and Lu, 2004b). More recently, distributions have been used in modelling bacterial survival to reflect an assumption that lethal events are probabilistic rather than deterministic. Survival of individual cells then follows a distribution; the Weibull distribution is the most commonly used, with the survival curve represented by the cumulative distribution function (CDF) and the Weibull parameter (β) well able to represent differing mechanisms of inactivation (Van Boekel, 2002, cited in McKellar and Lu, 2004b). A software tool, GInaFit, has been developed to fit a variety of inactivation curves to data (Geeraerd *et al.*, 2005; see also Section 5).

4.2.3.2 Secondary models

There are relatively few models that consider the effects of multiple environmental factors on the rate of death of microorganisms (Ross and Dalgaard 2004). Variability in non-thermal inactivation rates due to combinations of growth-limiting pH and a_w have been largely explained by variations in temperature and are reported to follow an Arrhenius equation (Ross *et al.*, 2008). Interestingly, the slope of the Arrhenius plot, i.e. the relationship between inactivation rates and temperature, was not significantly different for sets of *E. coli* and *L. monocytogenes* strains.

As with secondary growth models, many secondary inactivation models tend to be based on polynomial equations. These are empirical models that are relatively easy to implement, where the aim is to achieve a good fit. Gamma-type models are also used, whereby each of the individual multiple effects are characterised (Coroller *et al.*, 2006; Mafart *et al.*, 2002). Although these inactivation models are still based on empirical observations, there is an attempt to give a biological interpretation. These models are flexible, and allow the incorporation of additional factors.

Artificial neural networks have also been used for modelling the effect of multiple factors on inactivation. It has been suggested that this learning-based non-linear modelling technique describes interacting effects more accurately than traditional predictive microbiological models (Esnoz *et al.*, 2006); however, such neural networks are often based on a large number of parameters.

4.2.3.3 Processing models

In commercial manufacturing processes such as canning or continuous flow systems, where heat is used to pasteurise or sterilise food, the assumption of isothermal conditions used for predictive microbiological studies no longer holds. In order to deal with the non-isothermal conditions seen in these processes, Bigelow's model has been the standard for the low-acid canned food industry for many decades. This allows for the calculation of an integrated lethal effect, integrating the exposure time at various temperatures to time at a reference temperature, which enables processors to demonstrate that the required lethal effect is achieved over a number of different time and temperature combinations (Bigelow 1921, cited in McKellar and Lu, 2004b). In processes where there may be more variability in the temperature experienced by microorganisms than in a well-mixed batch system, e.g. due to differing speeds of product through a processing line or relative distance from the heat source, there is advantage in using more complex heat transfer models. These can be particularly useful when combined with predictive microbiological models and stochastic risk assessment model techniques (Membre *et al.*, 2006). The common alternative of using worst-case assumptions about inactivation effects, while erring on the conservative side with respect to microbial food safety, can also lead to the over-processing of food, with a subsequent decline in quality and a higher energy use.

Although thermal treatment remains the predominant method for processing foods, the demand for fresher, less processed products has led to the development of new technologies (McKellar and Lu, 2004a). Some of these are based on temperature, such as microwave and ohmic heating, whereas others such as high pressure, pulsed electric field, pulsed or ultraviolet light and ultrasound rely on other mechanisms of inactivation. Current models for non-thermal inactivation technologies are scarce and tend to assume first order kinetics.

4.2.4 Models of recontamination

During food processing, non-contaminated food products can also become contaminated from external (environmental) sources, or due to contact with contaminated food products, hands, cutlery or food processing equipment. This is particularly regarded as a problem if a processed food, which is free of pathogens, is recontaminated after processing.

Recontamination has recently been discussed by Reij *et al.* (2004), who give an overview of available models and discuss the role of recontamination in outbreaks originating from sources in the food chain. They describe various routes and sources of recontamination: raw materials, food contact surfaces, airborne contamination, pests and the food processing environment. Recontamination can occur during industrial food processing, at retail and during food preparation, either in the domestic setting or in professional kitchens.

Recontamination is infrequently incorporated in MRAs. This limited attention to recontamination could be due to a general lack of knowledge about the recontamination dynamics, a lack of data and exclusion of recontamination from the statement of purpose guiding the MRA.

Nevertheless, several models on recontamination have been used in risk assessments. In such models, the term "cross-contamination" is frequently used to describe the (re-)contamination of food products by microorganisms originating from other food products, either by direct contact or by indirect contact via food processing equipment, hands, etc. For example, if a machine surface is contaminated, microorganisms can be transferred to the product if a contact occurs between the machine surface and the product. This contamination can be modelled using a transfer rate and the probability of transfer for a single colony-forming unit (cfu) on one surface to be transferred to another surface. An increasing amount of such data on transfer of bacteria during food handling and the effects of washing has recently become available (e.g. Chen *et al.*, 2001; Montville *et al.*, 2001; Kusumaningrum *et al.*, 2004; Luber *et al.*, 2006; Schaffner and Schaffner, 2007; de Jong *et al.*, 2008; van Asselt *et al.*, 2008; Nauta *et al.*, 2008). There are several examples of models to be used in risk assessments. den Aantrekker *et al.* (2003a, b) modelled recontamination in factory environments. A model of cross-contamination during smearing of cheeses was proposed by Aziza *et al.* (2006). Cassin *et al.* (1998) defined a model for the effect of cross-contamination during industrial processing of beef, Schaffner (2004) a model for *Listeria* cross-contamination, and Nauta *et al.* (2005) developed a model for cross-contamination during industrial processing of chicken meat, which has also been adapted for pig slaughtering (Titus, 2007). These models have a varying degree of complexity, related to the process modelled and the purpose of modelling.

Recently, several risk assessments have focussed on cross-contamination in the domestic setting. This was led by the observation that exposure to meat-borne pathogens often occurs consequential to exposure via a ready-to-eat meal that had become contaminated during food preparation via indirect contact with contaminated raw meat. This route of exposure is particularly considered relevant for *Campylobacter* on chicken meat (Brynestad *et al.*, 2008; Calistri and Giovanninni, 2008; van Asselt *et al.*, 2008, Nauta *et al.*, 2009).

4.2.5 Models of mixing and partitioning

Apart from the above described models, risk assessments typically need to describe mixing and partitioning of units of food products (Nauta, 2008).

When food products are mixed, various units are joined together (e.g. when milk from different cows is assembled in a milk tank, or cuts of different carcasses are joined for grinding). As a consequence of this process, microorganisms are redistributed, resulting in an increase in prevalence and a decrease in the mean concentration in contaminated food units. An ILSI Europe Report (Bassett, 2010) identifies this process as "joining", and additionally characterises "mixing" as the process where microorganisms are redistributed over the product because of a rearrangement as a consequence of, for example, shaking or stirring.

With partitioning (fractioning), larger food units are split up into smaller ones (e.g. when milk is distributed into bottles, or ground meat is divided into patties). Here, the redistribution of microorganisms could result in a lower prevalence and a higher concentration in contaminated food units.

Although these processes do not result in an increase or decrease in the number of microorganisms in the total amount of food produced, they change the distribution of microorganisms over food items. This has an impact on the variability of doses between servings, and therefore may have an impact on the risk assessment. Models for mixing and partitioning are discussed by Nauta (2005), and involve the consequences of non-homogeneous mixing and dependence between food units. The importance of these processes and their impact on the distribution of the cells within the food products is extensively described in a report by ILSI Europe (Bassett, 2010).

4.3 Models for hazard characterisation

Various models used for dose–response relations are described in Buchanan *et al.* (2000), Buchanan *et al.* (2009), Teunis *et al.* (1996), Teunis *et al.* (1999) and Zwietering and Havelaar (2006). The basic model is the single-hit model, in which *r* is assumed identical for all microorganisms in the ingested dose, as described in Section 2.2.2:

$$P_{ill}(d,r)=1-(1-r)^d$$

Assuming that the microorganisms are homogeneously distributed; and therefore the exact dose in a serving of food is related to the average dose following a Poisson process, this results in the exponential model (Haas *et al.*, 1999):

$$P_{ill}(d,r)=1-\exp(-D \cdot r)$$

If it is assumed that the infectivity is not a constant but variable, then the Beta-Poisson model can be derived (Haas *et al.*, 1999). If the host variability is also included, then the Weibull–Gamma model can be derived (Buchanan *et al.* 2000). Often the quality of the data and the large uncertainty in representativeness of dose–response data do not warrant the use of more complex dose–response models.

4.4 Models for risk characterisation

In risk characterisation, the probability and severity for a given population or group of products is determined by combining all information from hazard identification, hazard characterisation and exposure assessment. No specific models are used here.

5. SOFTWARE TOOLS FOR MICROBIOLOGICAL RISK ASSESSMENT

Avariety of software tools to support MRA have been made available. Here we give an overview of risk modelling software; tools for hazard identification, risk ranking and prioritisation of risks; predictive modelling tools; tools for specific risk assessments; risk assessment information resources; and other tools. Finally, some software tools are presented that are currently being developed and are expected to be publicly available in 2012. Each tool is described briefly, and a reference is given that directs readers to the tool or provides additional information.

5.1 Risk modelling software

Software tools for risk modelling can be divided into three main categories:

1. Spreadsheet (Excel)-based software or other specific risk assessment software that is developed for risk assessment and stochastic simulation.

2. General simulation software, programming languages, mathematical modelling software and statistical software. These require more advanced programming skills and are not specifically developed for doing risk assessment.

3. Specific software for Bayesian analysis or otherwise.

Table 1: Software applied for quantitative microbiological risk assessment

Software	From	Type	Comment
[1]@Risk	Palisade www.palisade.com	Risk assessment software, add-on to Excel spreadsheet – simulation	Traditionally widely used for published QMRAs
[1]Crystal Ball	Oracle	Risk assessment software, add-on to Excel spreadsheet – simulation	Less frequently used for QMRA
[1]ModelRisk	Vose Software BVBA www.vosesoftware.com	Risk assessment software, add-on to Excel spreadsheet – simulation	Released 2009
[1]Analytica	Lumina www.lumina.com	Visual tool for decision models	Clear graphical interface, frequently used
[1]ExtendSim	Imagine that www.extendsim.com	Simulation software	Frequently used in non-microbiological risk assessment
[1]Arena	Rockwell Automation www.arenasimulation.com	Simulation software	Used for (industrial) process simulation and optimisation
[2]R	Freeware www.r-project.org	Statistical computing language	Frequently used for mathematical modelling, increasingly used in risk assessment
[2]Mathematica	Wolfram www.wolfram.com	Modelling, computing, simulation, mathematics	Frequently used for mathematical modelling, also for risk assessment

[2]SAS	www.sas.com	Modelling, simulation, statistical analysis, Bayesian analysis	Frequently used for mathematical modelling and statistics, also for risk assessment
[2]MatLab	Mathworks www.mathworks.com	Technical computing language	Frequently used for mathematical modelling, also for risk assessment
[3]WinBugs	MRC Biostatistics Unit www.mrc-bsu.cam.ac.uk/bugs	Bayesian analysis, Markov chain Monte Carlo	–
[3]Hugin	Hugin Expert www.hugin.com	Bayesian belief networks	–

[1, 2, 3] Indices indicate the number of the category of software tools, as given above the table.

5.2 Tools for hazard identification, risk ranking and prioritisation of risks

Risk Ranger

http://www.foodsafetycentre.com.au/riskranger.php
Ross and Sumner (2002)

Risk Ranger is a simple food safety risk calculation tool intended as an aid to determining relative risks from different product, pathogen and processing combinations. It provides a simple and quick means to develop a first estimate of relative risk. In addition to ranking risks, Risk Ranger focusses the attention of the users on the interplay of factors that contribute to foodborne disease. The model can be used to explore the effect of different risk-reduction strategies, or the extent of change required to bring about a desired reduction in risk. The model can be used by risk managers and others without extensive experience in risk modelling and can be used for helping to train food safety managers to understand risk.
Free download

sQMRA tool

http://www.foodrisk.org/exclusives/sQMRA/
Evers and Chardon (2010)

The sQMRA tool (for "swift" QMRA) can be used for quickly obtaining relative risk estimates of pathogen–food combinations, and can serve as a guide for risk management or for selection of combinations for applying traditional QMRA.
Free download

Semi-quantitative risk-ranking framework prototype
Newsome *et al.* (2009)

This functional semi-quantitative risk-ranking framework prototype is a flexible tool that enables relative comparison and ranking of microbial food-related risks with chemical risks via a single metric for overall disease burden: the annual pDALY (pseudo disability adjusted life years). The pDALY is a harmonisation of the very different dose–response relationships observed for chemicals and microbes that allows for a semi-quantitative characterisation of the disease burden of health impacts. This risk-ranking prototype is capable of assessing microbial hazards and chemical hazards not only separately, but also comparatively by using a common metric.
Available via the authors

Foodborne Illness Risk Ranking Model

http://www.thefsrc.org/firrm.htm#Installing%20the%20Model

The Foodborne Illness Risk Ranking Model (FIRRM) is a decision-making tool used to examine the public health burden of foodborne illnesses due to microbiological hazards from specific food commodities. Users can rank pathogen–food combinations by different measures of annual disease burden, as well as by estimated costs of illness and QALY (quality adjusted life year) loss.
Free download; requires Analytica

FDA's fresh produce risk ranking tool

http://www.foodrisk.org/exclusives/RRT/
US Food and Drug Administration

This is a semi-quantitative risk ranking tool to identify priority pathogen–produce commodity combinations based on explicit data-driven risk criteria. It provides a customisable and systematic means by which to prioritise pathogen–produce commodities for more rigorous quantitative MRA efforts.
Free download; requires Microsoft Office Access

5.3 Predictive modelling tools (to be used for exposure assessment)

Pathogen Modeling Program

http://pmp.arserrc.gov/PMPOnline.aspx

The Pathogen Modelling Program (PMP) is a package of models that can be used to predict the growth and inactivation of some foodborne pathogens under various environmental conditions. Predictions are based on specific papers, predominantly from US authors.
Free download

ComBase

www.combase.cc

ComBase is a database that comprises thousands of microbial growth and survival curves that have been collated in research establishments and from publications. They form the basis of microbial models presented in ComBase Predictor (a set of 23 growth models and six thermal death models for predicting the response of many important food pathogenic and spoilage microorganisms to key environmental factors). ComBase also contains the Perfringens predictor (an application for predicting the growth of *Clostridium perfringens* during the cooling of meats), and the ability to fit predictive models to data defined by the user.
Free access

DMFit

www.ifr.ac.uk/safety/DMFit

DMFit is a software package (an Excel add-in) that can be used to estimate the specific growth rates from experimental data with the Baranyi model (Baranyi and Roberts, 1994). DMFit is part of the system used in-house at the Institute of Food Research to model the time variation of the logarithm of cell concentrations of bacterial batch cultures. It has been the main tool in the development of the models behind ComBase Predictor (see above).
Free download

Microbial Response Viewer

http://mrv.nfri.affrc.go.jp/#/Home
Part of them form the basis of microbial models *C. perfringens* Koseki (2009).

The Microbial Response Viewer is a web-based database consisting of bacterial growth/no growth data classified from ComBase, using specific criteria.
Free access

Sym'Previus

http://www.symprevius.net

Sym'Previus is a collection of tools for food safety inspections designed for food sector businesses to help strengthen HACCP plans, develop new products, better understand and quantify microbial behaviour, determine shelf lives and improve food safety.

Accessible after subscription

Seafood Spoilage and Safety Predictor

http://sssp.dtuaqua.dk

The Seafood Spoilage and Safety Predictor (SSSP) software has been developed to facilitate the practical use of mathematical models to predict shelf-life as well as growth of spoilage and pathogenic bacteria in seafood, and to evaluate the effect of constant or fluctuating temperature storage conditions.

Free download

Forecast

http://www.campden.co.uk/services/predictive-microbiological-models.pdf

Forecast is a predictive modelling tool developed by Campden BRI for growth of spoilage organisms in foods. It includes models for fish, meat, fresh produce and yeasts in fruits and drinks, plus a range of models relevant to acidified foods.

Commercially available

MLA refrigerator index calculator

http://www.foodsafetycentre.com.au/refrigerationindex.php

Meat and Livestock Australia (MLA)

The refrigeration index (RI) is an index for the log growth of *E. coli*. It predicts the expected growth of *E. coli* on meat from temperature and other data. The central idea of the RI is to measure the performance of the chilling process until all the sites of microbiological interest are at or below 7°C. The RI, as an indication of the effectiveness of refrigeration, is NOT a prediction of the number of *E. coli* in the product.

Free download

MLA *E. coli* inactivation in fermented meats model

http://www.foodsafetycentre.com.au/fermenter.php

Meat and Livestock Australia (MLA)

This is a model for the inactivation rate of *E. coli* derived from analysis of a collation of data, that describe the fate of *E. coli* in uncooked, comminuted, fermented meat products or analogous environments in which low water activity or pH exist, or both.

Free download

GInaFit

http://cit.kuleuven.be/biotec/downloads.php

Geeraerd *et al.*, 2005

GInaFit is a tool for testing nine different types of microbial survival models on user-specific experimental data relating the evolution of the microbial population with time. It can help the end-user to communicate the performance of food preservation processes in terms of the number of log cycles of reduction rather than the traditional *D*-value.

Free download

AMI process lethality determination spreadsheet

http://www.amif.org/ht/d/sp/i/26870/pid/26870

American Meat Institute (AMI) Foundation

This is an Excel spreadsheet that provides meat processors with a science-based validation tool to demonstrate the effectiveness of a specific heat process to destroy a microorganism of concern, on the basis of a time–temperature profile. Developed for the American Meat Industry Foundation. *Free download*

5.4 Tools for specific risk assessments

JEMRA *Enterobacter sakazakii* in powdered infant formula model

www.mramodels.org/ESAK/RunModel.aspx

Joint FAO/WHO Expert Meetings on Microbial Risk Assessment (JEMRA)

The model is a user friendly risk assessment tool for powdered infant formula (PIF) that is contaminated with *Cronobacter* spp. (formerly known as *E. sakazakii*). The risk assessment explicitly examines the impact of different preparation and handling strategies of *Cronobacter* spp. in PIF and describes the outputs in terms of the relative risk posed to infants. It provides tools to explore the possible impact of microbiological criteria through the specification of sampling plans for *Cronobacter* spp. in PIF. *Free access*

Australian risk assessment model for *L. monocytogenes* in ready-to-eat meats

http://www.foodrisk.org/exclusives/models/AU_listeria.cfm

Ross *et al.*, 2009.

This is a risk assessment model that predicts the concentrations of *L. monocytogenes* on products at the time of consumption using industry and other survey data augmented by predictive microbiology models. *Free download; requires @Risk*

JEMRA (FAO/WHO) risk management tool for control of *Campylobacter* and *Salmonella* spp. in chicken meat

http://www.mramodels.org/poultryRMTool/.

Joint FAO/WHO Expert Meetings on Microbial Risk Assessment (JEMRA)

This is a risk management simulation tool based on the Codex Guidelines for the Control of *Campylobacter* and *Salmonella* in chicken meat, describing the complete production-to-consumption flow pathway. The tool is designed to compute the residual risk between a baseline process flow and a process flow applying selected interventions as outlined in the guidelines. The residual risk measure may be used to evaluate the overall effectiveness of the applied interventions.

5.5 Risk assessment information resources

FoodRisk.org

http://www.foodrisk.org

Joint Institute for Food Safety and Applied Nutrition (JIFSAN)

The aim of FoodRisk.org is to assist professionals involved with the many aspects of risk analysis as it pertains to the safety of food. The website provides data, tutorials, tools and links to numerous sources of information. *Free access*

5.6 Other tools

ICMSF sampling plan tool

http://www.icmsf.org/
International Commission on Microbiological Specifications for Foods (ICMSF)

This is a spreadsheet tool to explore ICMSF recommendations for microbiological sampling plans, based on ICMSF Book 7 (ICMF, 2002) and van Schothorst *et al.* (2009)
Free download

Food Handling Practices Model

http://www.foodrisk.org/exclusives/FHPM/

The Food Handling Practices Model (FHPM) is a computer simulation model that allows users to estimate how one or more changes in food handling practices at the retail, foodservice or household level might affect the annual number of food-related illnesses in the USA. The model operates by simulating, tracking and counting servings of food that become contaminated with one or more pathogens, followed by survival and growth of pathogens and subsequent ingestion that results in foodborne illness. The model does not track or count servings of food that are not contaminated with pathogens.
Free download; requires @Risk

FARE Microbial

http://www.exponent.com/fare_software/
Exponent Inc.

FARE Microbial is a software program for conducting probabilistic MRA. The program was developed by Exponent together with the US FDA, and consists of a contamination and growth module and an exposure module. It links food consumption patterns and exposure distributions. It incorporates algorithms developed by the FDA for the *L. monocytogenes* risk assessment, but is capable of performing risk assessment for a variety of foodborne pathogens.
Available via foodrisk.org

5.7 Upcoming tools

ICRA

Will be made available via http://www.foodrisk.org.

The webtool ICRA (Interactive Catalogue for Risk Assessment) is a "risk assessment information resource" that provides detailed comparative information on published risk assessments and is designed to be used by risk assessors who are developing a food chain QMRA.

JEMRA (FAO/WHO) sampling tool

Will be made available via http://www.mramodels.org.

This is an "other tool" to estimate the impact of microbiological sampling plans.

iRISK (FDA)

Will be made available via http://www.foodrisk.org.

iRISK is a web-based tool for "hazard identification, risk ranking, prioritization of risks", which can compare and rank risks from multiple food–hazard combinations, calculate public-health outcomes of variations in processing or handling practices and target interventions at all steps in the food supply chain from farm to home. It is the second generation of the semi-quantitative risk-ranking prototype mentioned in Section 5.2.

6. IMPORTANT CONCEPTS IN THE INTERPRETATION OF MICROBIAL RISK ASSESSMENT RESULTS

*D*epending on the context, complexity and purpose of a scientific assessment of risk (i.e. the risk question), the scope of an assessment may or may not involve a full risk assessment, and the methods and tools used may vary. As described in previous sections, results may be qualitative, semi-quantitative or quantitative, and they may represent the outputs from specific tools (e.g. PMP, risk ranking software), specific stages of a risk assessment (e.g. an exposure assessment) or a complete microbial risk assessment (i.e. resulting in risk characterisation). Despite these differences, there are common issues that need to be considered when interpreting the results from risk assessments or other scientific assessments related to risk. Since results are intended to inform decisions, some sort of evaluation in relation to the scope and quality of the assessment has to be made, i.e. that the assessment is "fit-for-purpose". This section contains a general description of important concepts necessary for understanding the outputs from various types of assessments of risk and risk assessment tools as well as descriptions of factors and criteria related to evaluating the validity and utility of risk assessments.

6.1 Qualitative and quantitative assessments

As discussed in previous sections, two broad categories of analyses within the context of the Codex risk analysis framework have been used: qualitative and quantitative MRA (Wooldridge, 2008). The same quality requirements should be used for qualitative as for quantitative MRAs in terms of statistical inference, data, models, documentation and transparency (Lammerding, 2007). This is true also for qualitative risk assessment schemes developed in the form of risk assessment matrices. Although attractive due to their apparent simplicity and user friendliness, it is important to be cautious of their possible limitations. Limitations that have been identified include the requirement for a detailed and relevant knowledge of the risk by the user, problems in defining categories and mathematical challenges combining discrete categories of probability and severity (Lammerding, 2007; Cox, 2008).

6.2 Variability and uncertainty

Probabilistic risk assessment models address the uncertainty and/or the variability of input data by describing model inputs using probability distributions (CAST, 2006). In order to interpret the results, it is important to know what the input distributions represent: variability, uncertainty or a mixture of both. The need to separate variation and uncertainty, e.g. by using second order Monte Carlo models, has been emphasised (Nauta, 2000). Failure to do so may lead to improper estimates of risk. A review of approaches to separate uncertainty and variability is given in the FAO/WHO exposure assessment guidelines (FAO/WHO, 2008).

There are many types of uncertainty in risk assessments, including process uncertainty, model uncertainty, parameter uncertainty and statistical uncertainty, and even uncertainty in variability (FAO/WHO, 2008). Process uncertainty refers to uncertainty about the relationship between the food chain as documented in the assessment and the processes that take place in reality. For example, rare, undocumented events in food production or consumer behaviour may have a relevant impact on the exposure without being fully considered in the model. Model uncertainty

is related to the way the complexity of the food chain is simplified, and the correctness of all the sub-models that are used in the exposure assessment. To enable the construction of the food chain model, process simplification is inevitable, but the level to which this is appropriate is subjective. Parameter uncertainty incorporates uncertainties dealing with errors resulting from the methods used for parameter estimation, like measurement errors, sampling errors and systematic errors. Statistical uncertainties are the result of stochastic fluctuations arising from the fact that a measurement is based on a finite set of observations.

Many types of uncertainty, for example model uncertainty, are difficult to quantify. In some cases, only those uncertainties that can be reasonably quantified are incorporated in the assessment, and it is then incorrectly assumed that uncertainty has been quantified. Often this uncertainty is then assumed to be the only source of uncertainty, while others have simply been neglected.

It is important to realise that variability occurs at many levels. Thus, there may be variability in genotype, strain type, time, place, experimental conditions, etc. It is therefore crucial that the denominator of the variability is defined (e.g. variability per year and variability per flock), and that variability from different sources is not mixed without careful consideration (FAO/WHO, 2008).

Variability is important in risk assessment because final population risk is given by the mean risk as calculated from a distribution describing the variability of ingested doses. Thus, the mean risk will determine the risk associated with the population of consumers or products, etc. Hence, after variability and uncertainty are separated in the analysis, it is important that the results are translated or interpreted so that implications for the risk managers and their decisions are clear. Individual variability may be specifically relevant for a risk manager wanting to protect specific risk groups. Whereas variability may not show up with the calculation of the population risk, uncertainty always remains (unless in future more or better knowledge is present), and the manager has to take that lack of precision into account when making and communicating his/her decision.

6.3 Sensitivity and uncertainty analysis

In order to interpret the results of a risk assessment it is important that the influences of the parameter estimates and assumptions on the results are demonstrated (CAST, 2006). For quantitative risk assessment, this can be done using sensitivity and uncertainty analyses. Uncertainty analysis and sensitivity analysis (sometimes called importance analysis) are two tools available that can be used to inform the risk manager about the outcome of the risk assessment.

A sensitivity analysis determines the degree of influence a given input or variability of an input has upon the value or variability of the output and, thus, aids in determining steps in the process where additional data collection is most useful, where monitoring of critical steps in the process is of greatest value and where mitigation strategies could be most efficient. Methods for sensitivity analysis have been reviewed and evaluated in Frey and Patil (2002).

Uncertainty analysis is designed to determine the contribution of the uncertainty associated with an input parameter to the degree of uncertainty in the risk estimate. The degree to which the uncertainty in a model output is affected by the uncertainty in the model input can be used to rank uncertainties. This information can be useful to focus research or data collection activities that could lower the model output uncertainty most efficiently.

6.4 Sources and magnitudes of uncertainty and variability in predictive microbiology

In QMRA, predictive microbiology models are commonly used to fill in data gaps that would otherwise require more extensive data collection programmes. For example, although the number of pathogenic bacteria in food at retail may be available, the number in the food immediately prior to consumption usually is not. It is important to understand that predictive microbiology models have limitations, e.g. uncertainties surrounding predictions are not always given, and predicted values may not truly represent the real world if models have not been validated (FAO/WHO, 2008). The limitations derive from methodological limitations, from model design limitations and from the food/microorganism system that is to be modelled (Ross, 1999). The most important of the methodological errors in terms of contribution to total error of predictive models are homogeneity errors and completeness errors. Homogeneity errors arise because at the microscale most foods are inhomogeneous in terms of conditions experienced by microorganisms and most current models do not account for this. The completeness errors arise because the model represents a simplification of reality and for practical reasons only a limited number of environmental factors can be included, e.g. models may not include food and microbial ecology effects (structure, competition, etc), which are difficult to quantify (Ross, 1999). Additional types of errors, in descending order of contribution to total errors, are model function errors, measurement errors and numerical procedure errors.

Two measures of model performance commonly used are the accuracy factor, A_f, and the bias factor, B_f (Ross, 1996). The accuracy factor indicates the average spread of observations around predictions. The bias factor indicates the systematic over or under-prediction of the response time of the model. A perfect model has a B_f of 1.0, whereas a B_f of 1.1 indicates that the model predicts longer times ($B_f < 1.0$ predicts shorter times) than observed, on average by 10%.

As discussed by Nauta (2002), it is important to realise that a quantitative microbiological growth prediction has usually different demands than a "traditional" predictive food microbiology growth model prediction. Thus, it may not be straightforward to apply the available predictive microbiology growth models in stochastic QMRA studies. Predictive growth models are generally developed and validated as models that give point estimates, commonly with confidence intervals based on experimental or biological variability, but not as stochastic models. Confidence intervals should always be carefully interpreted, since they can be based on variability, uncertainty or some mixture of the two.

For example, PMP and the ComBase predictor in the ComBase toolbox (see Section 5) allow predictions of microbial processes to be made. The data behind these predictions were collected using broths of different compositions and usually a cocktail of strains. Some of the models may have been validated in specific food types but this information is not directly accessible to the user, who needs to do a literature search. The predictions of PMP are given with a 95% confidence interval, whereas those of ComBase are given as point estimates. The confidence interval of the PMP models reflects the statistical and experimental errors associated with the setup and strain(s) used to develop the broth model. Thus, the interval is a mixture of uncertainty and variability, and there are possibly important factors not reflected in the confidence interval, e.g. the extent of strain variation in nature. Usually either one strain or a cocktail of strains are used in these studies. Therefore, variation among strains would not be considered in the first case, or would only show the strain with fastest growth or higher resistance in the second case.

6.5 Fit for purpose: utility and validity

The most important attribute of an MRA is that it is "fit-for-purpose", i.e. that it answers the risk management question(s), improves the decision-making process and does so in a timely manner (Lammerding, 2007; Dennis *et al.*, 2008). The most appropriate approach and type of MRA will vary depending on the nature of the problem, its context and complexity, the uptake of the MRA outcomes, the urgency of the risk management decision, the involvement of stakeholders and other factors. For instance, unique, wide-impact decisions to inform single-time decisions that impact the health of large numbers of people over long periods of time are typically controversial, with disparate perspectives on the nature and extent of the risk, and will probably require a different risk assessment process than routine, narrow-impact decisions that involve risk assessments similar to those performed previously (USEPA, 2000). Thus, complex (e.g. stochastic, quantitative) as opposed to simple (e.g. deterministic, qualitative) approaches to risk assessment are not by definition better, and both approaches have their merits (Zwietering, 2009). The analysis should be made as simple as possible while still maintaining an appropriate representation of the problem at hand and giving meaningful risk assessment results (Morgan and Henrion, 1990).

The timeframes and available resources determine the stringency of the assessment and this may have implications for the quality of the MRA. This underlines the need for effective interactions between risk managers and risk assessors to make it clear what stringency needs to be built into an MRA. It is evident that many of the current food safety problems are very complex, leading to complex risk questions, and this together with the complexity of the food production chain will often require a full QMRA approach and many different kinds of data (Havelaar *et al.*, 2008).

The process of assuring the quality of an assessment (or an assessment tool) should be addressed in advance of the development. However, the same principles and factors can be considered by a user or manager when evaluating the results and the quality of an assessment. Key principles and concepts that have been proposed relate to transparency, clarity, consistency, reasonableness, validity and utility (EFSA, 2009; USEPA, 2000; Lammerding, 2007). The utility and validity of an MRA were defined in the ILSI workshop in Prague as two important aspects of fit-for-purpose (Lammerding, 2007). Utility relates to the usefulness regarding the purpose an MRA has been developed for and validity relates to the trueness or correctness of an MRA. Factors and criteria related to the validity and utility, respectively, of an assessment and an account of some important aspects to consider when interpreting the results from a scientific assessment are described in Tables A1 and A2 in the Appendix (see pages 31 and 32). Although these criteria are presented separately, in practice, the validity and utility are both multidimensional and overlapping and are best considered together.

6.6 Interpreting the results of an assessment of risk

A standard set of guidelines for interpreting the results of an assessment of risk does not currently exist. Due to the variation in types of assessments and tools it is hard to be prescriptive. However, as pointed out by Lammerding (2007) the process of interpreting results needs to focus on activities that will evaluate the validity and utility of the assessment or tool. Put simply, in order to interpret the results, the evaluation should answer three questions:

1.   What is the purpose or objective of the assessment or tool?
2.   How is the assessment or objective carried out?
3.   What does the result mean in terms of implications for the user?

The relevant information as well as the extent of the evaluation will depend on whether the outcome is from a complete risk assessment, part of a risk assessment, a predictive microbiology model, a risk ranking tool, etc. Table 2 gives examples of information and questions to address in this process.

Table 2. Examples of information and questions to address when evaluating the validity and utility of an assessment or tool

Question	Comment/examples
What is the purpose or objective of the assessment or tool?	The answer to this question should be easy to obtain if the transparency and presentation of the assessment or tool is satisfactory, and would indicate its utility or applicability to the user and if it is worthwhile to continue the evaluation. Examples of information needed include: • What is the risk question(s)? • What basis will the decision be made on? • How will the result or outcome be used? • What is the context and outcome? • Which scenario(s) are addressed? • Which metrics/units are used? • What are the scientific assumptions and how were they addressed? • What are the policy choices and how were they addressed? • Which populations were considered?
How is the assessment or objective carried out?	To evaluate this question, methods, models, assumptions and data need to be scrutinised in order to come to a conclusion about the validity of the assessment or tool. Examples of information needed include: • What is the validity of science and logic in the assessment? • How were probabilities assigned and propagated? • Are the data used current, relevant and sufficient? • What is the rationale for data inclusion or exclusion? • How was the potential problem of bias treated? • How were the scientific assumptions addressed and justified? • Is the assessment consistent and systematic? • How was uncertainty treated and what is included in the uncertainty? • How was variability treated and what is included in variability? • How were predictive microbiology models used? Validated models and/or comparisons between models? • Were sensitive populations considered? How? • Are strengths and weaknesses identified in the assessment? How were they addressed? • Has there been a peer review?
What does the result mean in terms of implications for the user?	If the assessment is considered fit for purpose, an interpretation of the results and its implications need to be carried out if the output is to be used to inform decisions. Examples of information needed include: • Were the results put in perspective and are they consistent with observations or other similar results? • What is the confidence level of the result? • Which factors have the greatest impact on the outcome? • Which uncertainties have the greatest impact on the outcome? • Were mitigations evaluated and did the analysis indicate any differences between them? • What were the major conclusions in relation to the risk question? • Were stakeholders involved in the assessment? • Is there need for informing different audiences about the results? • Were knowledge gaps identified and evaluated?

Ideally, the final risk characterisation step presents an interpretation of the results of the risk assessment. This step integrates information from the preceding steps of the risk assessment and synthesises an overall conclusion about risk that is complete, informative and useful for decision makers. In essence, a risk characterisation conveys the risk assessor's judgment as to the nature and existence of …risks" (USEPA, 2000). Essential elements of the quality of a risk assessment are the use of good practices in terms of data, models and procedures, and how uncertainty and variability have been addressed. Crucial in promoting quality of the results are the transparency of the assessment and the peer and public review process. The principle of transparency should ensure that a reader understands the steps, logic, key assumptions, limitations and decisions leading up to the result (CAST, 2006). The process of peer and public review should be interdisciplinary to cover all relevant aspects in order to improve the credibility of the assessment.

6.7 Making decisions using risk assessments and risk assessment tools

A modelling approach is not only used to assess the risk but also to provide valuable information on the uncertainties associated with inputs and, thus, the available control options. Sensitivity or uncertainty analyses can be conducted to identify key contributors to variability and uncertainty in model outputs, in order to suggest targeting research efforts for the most important inputs. In addition, a simulation model can be used to analyse what-if scenarios as a basis for selection of risk management options. It should be realised that the decision maker or the risk manager make their analyses in a wider decision-making context. The risk assessment model or tool may provide decision support, although no hard decisions. In addition, formal decision analyses, such as multi-attribute analyses, cost–benefit analyses and utility-based analyses, are needed to take relevant criteria other than risk into consideration.

Although outcomes and results from risk assessments and risk assessment tools should not be considered absolute, and decisions should not be based solely on these outcomes, it is clear that these tools can fulfil an important role and improve food safety decisions. Uncertainty in the predictions or risk estimates may be great. However, this will in most instances be due to the nature of the questions and current knowledge and not due to "the tools". Furthermore, knowledge about the extent of uncertainty, although great, should be useful information to inform any decision.

7. APPENDIX

Table A1. Criteria relevant to validity

Characteristic	Comments
Timeliness	In response to the decision-maker's needs; will determine approach and stringency
Quality and treatment of data	Validity of science and logic; current, relevant and sufficient data; rationale for inclusion/exclusion of data
Inference of probability	Appropriate assigning and propagation of probabilities; appropriate choice of distributions; adequate number of iterations in a simulation model to detect rare events of concern In semi-quantitative or qualitative MRA, clear definition of the meaning of "descriptors" such as negligible, low, medium, high; logic in combining semi-quantitative values; clear description of how conclusions are derived and magnitudes of probability and severity are assigned
Internal consistency	Sound logic and inference; systematic reasoning; particularly important in assigning values for risk ranking and other non-mathematical evaluations
Appropriateness of assumptions, expert opinion, scientific support	Logical soundness of premises or underlying assumptions in scientific justification, in terms of theoretical arguments or empirical results, and in methodological assumptions
Epidemiological and biological credibility	Outcomes should not be inconsistent with observed data; although not necessarily in agreement should be within plausible limits and account for all observations
Transparency	Systematic development of the MRA steps and the MRA structure; the models used to describe the food supply chain, processes and microbiological dynamics; the data used and those disregarded as well as pertinent data gaps; the use of alternatives to close data gaps (e.g. expert knowledge, surrogate data, assumptions); the uncertainty in the models, data, assumptions as well as in the risk estimates and for the different "what-if" or mitigation scenarios developed; the process of reasoning to arrive at conclusions in qualitative MRA; documentation in adequate detail for appreciation by the variety of stakeholders
Peer-review[1]	Independent review of data, logic, scientific interpretation, models and analysis; may require different experts for different aspects of the MRA; staggered process for complex MRA – review of model at early stages of assessment process; guidance given to reviewers in the form of directed questions, access to model
Stakeholder involvement	As appropriate for inputs of data & knowledge about the risk situation; for government – to ensure MRA reflects broad scope of an industry or public segments
Trustful outcome	Confidence level associated with results

[1] Generic guidance documents to help direct the peer-review process for risk assessments have been elaborated by different agencies, including the World Organization for Animal Health (OIE), the US Food and Drug Administration and the US Environmental Protection Agency (Lammerding, 2007).

Table A2. Criteria relevant to utility

Characteristic	Comments
Addresses the MRM question(s), timely, responsive	MRM "process" related, i.e. importance of communication and understanding between managers and assessors, clear definition of problem statement and scope, ultimate application of outputs; iterative interactions before and during the MRA
Stringency and detail	MRA approach/method and scope (e.g. qualitative or quantitative; food-chain vs. specific stage) and form of outputs should be appropriate for the importance of the task or decision required
Clarity for different audiences	Tiered series of reports for more than one group of people, ranging from complete analytical documentation to interpretive summaries aimed at non-technical audiences
Explicit statement of limitations	Clear description of constraints relevant to the accuracy, interpretation and application of results
Objectivity	Avoidance of language/conclusions that imply what the risk manager's decision should be
Proactive	Findings help to decrease risk, prior to product being released in the marketplace
Reactive	Findings help to understand how and where risks arose with products already in marketplace
Identification of risk-determining steps, knowledge gaps and conflicting evidence	Helps decision-makers to focus on important factors in the food chain for intervention, and informs both decision-makers and scientists about important data collection/data generation needs
Inclusion of "what-if" scenarios, evaluation of potential risk reduction strategies	Requires defining scenarios together with risk manager(s) prior to and/or during the conduct of the MRA (may also include economists at some early stage for cost–benefit/utility analysis considerations); iterative and interactive
Aids in prioritisation	Results inform decisions about where to allocate resources for optimal risk mitigation
Database of knowledge	A comprehensive compilation of data, information and assumptions relevant to a pathogen, food, host and exposure pathway(s), which can be updated with new knowledge
Applicable to stakeholders	The MRA enhances understanding of the food safety risk issue, and can inform participants (industry or trading partners) involved at different stages along the food chain; new information or insights may be used by stakeholders for other purposes; helps to promote communications
Adaptable to other countries	Particularly relevant for government and international (e.g. FAO/WHO) MRA; may be feasible for countries with comparable industries and host populations to adopt or adapt as is appropriate using local national data

(Lammerding, 2007)

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