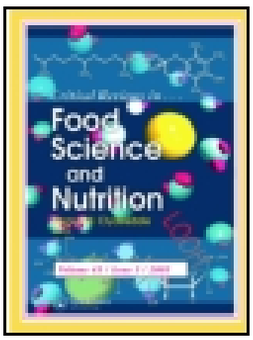

Taylor & Francis
Taylor & Francis Group

Critical Reviews in Food Science and Nutrition

ISSN: 1040-8398 (Print) 1549-7852 (Online) Journal homepage: https://www.tandfonline.com/loi/bfsn20

A common approach for ranking of microbiological and chemical hazards in foods based on risk assessment - useful but is it possible?

R. Lindqvist, T. Langerholc, J. Ranta, T. Hirvonen & S. Sand

To cite this article: R. Lindqvist, T. Langerholc, J. Ranta, T. Hirvonen & S. Sand (2019): A common approach for ranking of microbiological and chemical hazards in foods based on risk assessment - useful but is it possible?, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2019.1693957

To link to this article: https://doi.org/10.1080/10408398.2019.1693957

Published online: 25 Nov 2019.

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
https://doi.org/10.1080/10408398.2019.1693957

Taylor & Francis
Taylor & Francis Group

REVIEW

A common approach for ranking of microbiological and chemical hazards in foods based on risk assessment - useful but is it possible?

R. Lindqvist[a], T. Langerholc[b], J. Ranta[c], T. Hirvonen[c], and S. Sand[a]

[a]Department of Risk Benefit Assessment, Swedish Food Agency, Uppsala, Sweden; [b]Faculty of Agriculture and Life Sciences, University of Maribor, Maribor, Slovenia; [c]Risk Assessment Research Unit, Finnish Food Safety Authority, Evira, Helsinki, Finland

ABSTRACT

This article compares and contrasts microbial and chemical risk assessment methodologies in order to evaluate the potential for a common framework for ranking of risk of chemical and microbiological hazards, and developments needed for such a framework. An overview of microbial (MRA) and chemical (CRA) risk assessment is presented and important differences are highlighted. Two microbiological and two chemical hazard-food combinations were ranked based on both a margin of exposure and a risk assessment approach. The comparisons illustrated that it is possible to rank chemical and microbiological hazard-food combinations with traditional approaches from each domain and indicated that the rank order but not the absolute measures is similar using either approach. Including severity in the assessment using DALY reduced differences between hazards and affected the outcome more than which approach was used. Ranking frameworks should include assessment of uncertainty as an integral part of the ranking, and be based on assessment of risk, not safety, and expressed in a common health metric such as disease burden. Necessary simplifications to address data gaps can involve the use of default scenarios. Challenges include comparisons of case-based *vs.* non-case-based health-endpoints, *e.g.* biomarker concentration, and integration of the severity of health effects into ranking.

KEYWORDS

Risk ranking; food safety; chemical hazards; microbiological hazards; DALY; risk prioritization

Introduction

In the current paradigm of applying risk analysis to food safety, management of safety issues should ideally be risk and science based. Other key values include transparency and the clear separation of the roles and responsibilities of risk assessors and risk managers, as well as the pivotal role of risk communication (FAO/WHO 2006; CODEX 2007). The disease burden due to chemical and microbiological hazards continue to be high and an impediment to socio-economic development (WHO 2015), and at the same time limited resources require a prioritization between problems. This situation has prompted initiatives for developing methods and data to support decisions on risk based prioritization and control, such as classification of food business operators (ANZFA 2001; FAO 2011), as well as schemes to compare and rank different hazards and foods (Newsome et al. 2009; EFSA 2012b; Chen et al. 2013). In relation to the need for transparency, attempts to communicate the outcome of risk assessments and risk rankings in common formats or metrics to managers and consumers/stakeholders have been published (EFSA 2015b; Sand et al. 2015; van der Fels-Klerx et al. 2015; BfR 2018). However, risk communication and risk management can become complicated if results are presented on different scales or have been evaluated by principally different conceptual methods with qualitatively and quantitatively different data. This can be potentially misleading for risk managers, consumers and other stakeholders and may even result in controversies, and possibly to less than optimal prioritization.

Methods used for chemical and microbiological risk ranking have been reviewed (Van der Fels-Klerx et al. 2018). Risk assessment was the most frequently used method for ranking and other methods were risk ratio, scoring, risk matrices and flow charts (decision trees and influence diagrams). These methods were mostly applied to chemical hazards. Additional methods used were cost of illness (CoI), health adjusted life years (HALY), and expert judgments, and these were mostly applied to microbiological hazards. The most important requirement for ranking of hazards is that it should be based on sound methods and data so that the outcome results and metrics truly reflect risk. Of concern in this respect is the observation that risk ranking outcomes of hazard-food combinations based on semi-quantitative scorings and full quantitative risk assessments, respectively, were not well correlated (EFSA 2015b). In addition, to be able to compare across hazard types, rankings need to be expressed in similar risk metrics and thus, ideally, be estimated based on similar conceptual

CONTACT Roland Lindqvist roland.lindqvist@slv.se Swedish Food Agency, P.O. Box 622, SE-751 26 Uppsala, Sweden.

frameworks. For instance, when exposure is compared to a health-based guidance value (HBGV) it may be argued that safety rather than risk of chemical hazards is assessed. Further, in using HBGV approaches severities of the health end points have not been considered to any great extent. Also, risk rankings should ideally be applicable to most hazard food combinations, with reasonable resource needs, and with the available data. Thus, there are inevitably tradeoffs between these requirements, and fully comparable metrics may not be feasible. The optimum solution may lie somewhere in the continuum between wholly subjective opinions to full quantitative risk assessments for all hazards/foods being ranked.

The purpose of this article is to compare and contrast microbial and chemical risk assessment methodologies in order to evaluate the potential for a common framework for ranking of risk of chemical and microbiological hazards and the developments needed for such a framework. The developments would aim for metrics more applicable for a common risk ranking which would facilitate risk communication to risk managers and other stakeholders, including consumers, in terms of transparency and consistency. This work is part of a project to explore and, if feasible, develop an approach for combined risk ranking of these classes of hazards and aims to identify and evaluate the main issues to address in this context. The specific objectives are to (1) give an overview of microbial (MRA) and chemical (CRA) risk assessment, (2) highlight important commonalities and differences, and 3) identify the main issues to address when developing common approaches for risk ranking of both classes of hazards, including the applicability of such a framework. The last objective is partly addressed by including case studies where the risks associated with chemical and microbiological hazard-food combinations are estimated using both a chemical and a microbiological risk assessment approach, respectively. The resulting rank-orders using the two approaches are then compared.

Overview of risk assessment methodologies

Risk analysis in the Codex Alimentarius Commission framework consists of risk management, risk communication and risk assessment (CODEX 2007). Clear roles and responsibilities are allocated to each of these three processes. In this framework, risk assessment should be a science based and transparent process only taking into consideration scientific evidence relating to human health in order to provide non-biased input to decision makers, *i.e.* risk managers. A principal difference between hazard and risk is acknowledged in both MRA and CRA. According to Codex (2007) hazard is a biological, chemical or physical agent in, or condition of, food with the potential to cause an adverse health effect, while risk is a function of the probability of an adverse health effect and the severity of that effect. In Principles and Methods for the Risk Assessment of Chemicals in Food, published in the context of the International Program on chemical safety (CODEX 2007; FAO/WHO 2009), hazard is defined as an inherent property of an agent or situation to cause adverse effects on an exposed organism or system, whereas risk is defined as a the probability of the adverse effects to take place under specific circumstances. Thus, without the explicit consideration of the associated severity. Overall, CRA and MRA follow the same basic four steps of hazard identification, hazard characterization, exposure assessment and risk characterization. The definitions and the terms used to describe the risk assessment process in this review follow CODEX (2007). Key in the assessment is to evaluate uncertainties related to input data, assumptions and modeling, and both deterministic and stochastic approaches are applied for this. Deterministic models use point values, often related to mean or other measures of central tendency in data or a theoretical mean, to provide one result for a given set of input values. In contrast, stochastic models use probability distributions that may reflect variability, uncertainty or both in the input data and predictions. The approach and data needed for a risk assessment is dependent on the risk management question(s) and the reason for doing an assessment. Therefore, initially the scope of a risk assessment should be defined and an unambiguous statement of the problem and its context developed. Depending on the risk assessment question, it may be important to address subpopulations at higher risk due to consumption patterns or predisposing physiological conditions.

Chemical risk assessment

Hazard identification

Chemical hazards can enter food at any stage including processing steps, and the weight of evidence for adverse health effects based on scientifically credible reports are evaluated and pathways that may lead to exposure are identified. Hazards are identified mainly based on experimental animal studies and human epidemiological studies, but also on in vitro tests and environmental studies.

Hazard characterization

This step involves qualitative or preferably quantitative descriptions of the relationship between the administered dose of, or exposure to, a chemical, and its health effects. For binary responses (*i.e.* a yes or no response per individual exposed) the health effect is expressed as a probability of effect, given exposure. For continuous responses such as the body weight or concentration of a biomarker, the health effect is the measured response in the exposed individuals. Required toxicity data are traditionally provided from controlled experiments with laboratory animals. These data provide the basis for determining the critical effect defined as "the first adverse effect or known precursor that occurs to the most sensitive species as the dose rate of an agent increases" (EPA 2002) for which an overall reference point (RP), also called point of departure (POD), is derived. The RP represents a starting point for further risk assessment, *e.g.* establishment of health based guidance values (HBGVs), for chemicals considered to have a threshold. The RP based on the critical health effect observed in the pivotal study is derived by the benchmark dose (BMD) approach, or

represented by the no-observed adverse effect level (NOAEL) (Crump 1984; Dourson et al. 1985; EFSA 2005; EPA 2005; EFSA 2009a; EPA 2012a; Hardy et al. 2017). Whenever the BMD method is applied, the lower confidence limit of the BMD (BMDL) is generally used as the RP to account for uncertainties. For development of a HBGV, assessment factors (AF) are applied to the RP to account for inter- (for uncertainty) and intra-species (for variability) differences in susceptibility. In the absence of chemical-specific data an overall assessment factor of 100 is used if the RP is based on experimental toxicity data (WHO/IPCS 1994). Additional considerations may modify the overall AF used, *e.g.* the route and duration of exposure in the critical study, and limitations of the database (EPA 2002, 2012a). For chronic (long-term) exposure, the HBGV is determined as a tolerable daily/weekly intake (TDI/TWI) for contaminants and as an acceptable daily intake (ADI) for substances with intended use, such as food additives and pesticides. The TDI/ADI corresponds in practice to the reference dose (RfD) or reference concentration (RfC) established by the EPA. HBGVs are not set for compounds that are both genotoxic and carcinogenic, and more generally when the critical dose-response relationship is suspected or considered not to have a threshold (EFSA 2010).

Exposure assessment

Dietary exposure assessment combines data on concentrations of chemicals in specific foods and food consumption recorded in dietary surveys. Consumption patterns and concentration levels of chemicals in different foods can lead to large differences in the exposure. Food handling may reduce some chemical exposures (*e.g.* washing, peeling) or increase the exposure to some compounds (*e.g.* frying, barbecuing). To address variability and uncertainty a range of values are generally presented as part of the exposure assessment, *e.g.* the mean/median as well as upper percentiles of exposures (*e.g.* the 95th percentile), for different population subgroups like adults and children. Resulting estimates may refer to acute exposure or long term usual exposure (*e.g.* average exposure per day). A distribution of usual exposures describes the variation between individuals in their usual exposures over an unspecified 'long' time span, not accounting for changes over age groups. A distribution of acute exposures describes the random single day exposures for an individual or population group.

Risk characterization

The final step combines information on hazard characterization with the exposure assessment to provide a qualitative or quantitative estimation of risk for a specific hazard to cause adverse health effects under different exposure scenarios. However, in practice "risk" is not directly addressed in CRA. Rather, the exposure is compared to the HBGV, and there may be a health concern if the estimated human exposure to a chemical exceeds this exposure guideline value. In the case of compounds that are both genotoxic and carcinogenic, a margin of exposure approach (MOE = RP divided by the estimated human exposure) is recommended by EFSA, and they consider that a MOE of 10,000 or greater would generally be of low concern (EFSA 2005). Variability and uncertainty in the risk characterization mostly reflects the exposure assessment side, since a single value, *i.e.* a HBGV or RP, is generally compared to several exposure estimates describing different subpopulations (that may also account for uncertainty to some extent). Stochastic methods have been suggested to account for both uncertainty and variability (Van Der Voet and Slob 2007; WHO/IPCS 2014).

Microbial risk assessment

Hazard identification

In contrast to CRA, it is generally known which biological agents, *i.e.* microorganisms and/or their toxin(s) have a potential to cause adverse health effects. This step is often more concerned with the next step of defining which microorganism(s), food(s), sub-population(s), or processes that are of relevance for the scope of the risk assessment. Thus, there is some overlap and similarities with a risk profile (CODEX 2007). However, the latter also involves risk management perspectives. Important information includes epidemiological investigations to indicate major sources of exposure and contributing factors leading to foodborne illnesses and outbreaks. This information can be further supported by clinical and microbiological evidence that may also indicate if sensitive populations exist. Surveillance studies may identify high-risk products or processes. Experimental and clinical studies can contribute insights about the nature and behavior of the hazard (Lammerding and Fazil 2000).

Hazard characterization

Characterization of adverse health effects caused by a foodborne microorganism involves the type and the severity as well as the duration of effects. Hazards can be differentiated based on their mode of pathogenicity into three broad classes, infectious; causing adverse effects after adherence, subsequent multiplication and invasion of the epithelium or other damaging effects, toxigenic; secreting pre-formed toxin in the food (food intoxication), or toxico-infectious; where the microorganism is secreting toxin after introduction into the host (Buchanan, Smith and Long 2000). The outcome of exposure, *i.e.* the response in terms of adverse health effects depends on the integration of properties of the microorganism, the food and the host. Microorganisms display variable capabilities to survive and grow in different foods, as well as to cause adverse effects in the host. This variability is evident both between and within microbial species. In addition, different human subpopulations may also display widely differing dose-response relationships depending on immunity in relation to previous exposure or the existence of risk groups with several orders of magnitude higher susceptibility (Pouillot et al. 2015). Published dose-response studies may consider different population subgroups than those in question. The food vehicle can impact both the survival and the virulence of a microorganism, *e.g.* by elevating the gastric pH barrier and by inducing the expression of specific genes (Gahan and Hill 2014). Dose response models for toxin

producing agents include probability of toxin production and threshold types of models, often with the threshold defined by the number of microorganisms considered necessary to produce significant amounts of toxin. For infectious agents the working hypotheses include non-threshold type of models assuming independent action of microorganisms and that one microorganism may be sufficient to initiate infection and illness. These single hit models are characterized by linearity in the low-dose region (WHO/FAO 2003). The end-point of the dose-response relationship may be infection, illness (commonly gastro-enteritis symptoms) or mortality. Conditional dose-response models have also been used, *i.e.* models describing the probability of illness given infection (Teunis, Nagelkerke and Haas 1999). Dose-response models can be based on data from human volunteer studies, animal data, epidemiological (outbreaks) data, expert knowledge elicitation or combinations of these data (WHO/FAO 2003). Despite of known sources of bias, assessment factors are generally not applied.

Exposure assessment

The data needed to estimate exposure include serving sizes and frequency of consumption of the relevant foods and this is combined with the frequency and concentration of contamination of the pathogen at the time of consumption. Data on the latter is usually missing. Instead data from preceding steps in the food chain is used and subsequent changes due to the biological processes of inactivation and growth or other non-biological processes such as partitioning, mixing/pooling, cross-contamination, addition, redistribution, evaporation/dilution and removal (Nauta 2001; Chen et al. 2013), are generally modeled using predictive microbiology, *e.g.* McMeekin and Ross (2002). Which part of the food chain that is included and modeled in the assessment, is determined both by the scope of the risk assessment and the data available to estimate exposure and risk. The growth of microorganisms in foods depends on intrinsic food properties (*e.g.* food composition, pH, water activity, potential antimicrobials) and extrinsic food parameters (*e.g.* storage temperature, humidity). A major challenge is to predict the lag phase duration, *i.e.* the adjustment time before growth starts. This will depend both on the prior, usually unknown, history of the microorganism affecting the physiological state, and the current environmental factors of the food. Knowledge of the prevalence and levels of the pathogen at one stage in the food chain may not be sufficient, since microorganisms can enter the food chain or their numbers may change at any step, *i.e.* primary production, processing, retail, transport and the consumer stage.

Risk characterization

The estimate of risk with associated uncertainties in the population of interest may be expressed as risk per serving or as annual population incidence per 100,000, or since the objective of a quantitative MRA may also be to evaluate risk mitigation options by running what-if scenarios, as relative risk between different intervention scenarios. In addition, sensitivity and uncertainty can be evaluated using different scenarios, assumptions, and distributions. Many common sources of uncertainties can lead to large uncertainties in the final risk estimates, especially when they are expressed as absolute risk. Although not rigorously tested, relative risk estimates may be more robust since common sources of uncertainties are expected to cancel out between scenarios.

Epidemiological considerations

Commonly both CRA and MRA apply a bottom-up approach, *i.e.* based on the occurrence of hazards in food servings and on the consumption, to estimate and rank risk. This approach has advantages in employing a detailed description of the entire pathway, but this may also be a limitation since uncertainties over several critical factors in the food chain can be prohibitive for accurate estimation of absolute population risk. Top-down approaches, based on epidemiological data on the occurrence of illness may also be employed in ranking of chemical and microbiological hazards. Epidemiological data can serve as input for all steps of the risk assessment process but they can also be used directly as a measure of final risk characterization. Before the incidences or the number of cases can be used as measures of risk, the inherent limitations of epidemiological data need to be addressed. These include the need for factors for underreporting/under-ascertainment of cases (van Lier et al. 2016), and the attribution of cases to the different transmission pathways, hazards and food sources being ranked. For the latter there is a need for combining several types of data to obtain source attribution (Pires 2013), or to estimate the effect of removing the exposure in order to estimate the population-attributable fraction (PAF) or risk (PAR) (Stafford et al. 2008). Chronic illness after long-term exposure, which is common for chemical hazards or sequelae following infection, raises particular difficulties when attributing cause-effect relationships. Further, chronic disease outcomes may also have multiple etiological factors. Likewise, infections of foodborne pathogens can be due to sources other than food. This inability to accurately link exposure and related disease consequences from public health data is a source of large uncertainties, especially for chemical hazards. Particularly if predicting long-term population effects based on current exposures that may well change over time. For this reason, a top down ranking approach is generally not used for CRA of hazards in food.

Important commonalities and differences between MRA and CRA

Since chemical and microbiological hazards may vary widely in their behavior (survival, growth, inactivation *vs.* persistence, transformation and other processes affecting the concentration of a chemical) and associated adverse health effects, substantial differences exist between CRA and MRA. The US EPA (2014) examined the applicability of chemical risk assessment methods to microbial risk assessment and concluded that many of the concepts developed for chemical

Table 1. A summary of general properties of chemical and microbiological hazards that are of relevance for risk assessment.

Property	Chemical hazards	Microbiological hazards
Nature of hazard	In practice continuous due to large number of molecules/atoms resulting in gradual effects, may accumulate in host over time	Discrete, smallest unit is one, can multiply, host can become carrier
Detection	Often at concentrations below levels of concerns	Detection of single cells often not possible
Type of health effects	Generally chronic	Generally acute
Epidemiology	Often no attributable (apparent) cases	Both outbreaks and single cases identified and attributed to hazard but less often to food
Dose response data	Continuous (*e.g.* a marker) or case based health effects	Generally case based health effects
Potential for control	Many hazards can be effectively controlled at the farm level	Many hazards cannot be effectively controlled at the farm level
Effect of processing (manufacturing, storing, preparation, etc.)	Generally not considered except for chemicals produced during processing (*e.g.* heat induced compounds, smoking)	Large effect on many microbiological hazards due to growth, inactivation, etc.
Regulatory maximum levels in food	Defined for many chemicals used in the food chain, but large groups not regulated	Not defined for most microbial hazards
Safety/assessment factors in risk characterization	Applied	Not applied
Dose-response modeling	Several models considered descriptively, no distinction between threshold and non-threshold effects at the level of the BMD.	Non-threshold approaches except for toxin producers,
Part of food chain modeled	Consumer phase only	Farm to fork or relevant parts of food chain
Processes modeled	Consumption	Many (*e.g.* biological such as growth, inactivation, toxin production, and physical processes affecting prevalence and concentration such as mixing, partitioning)
Guidance values	HBGV or reference point often applied	Microbial food safety criteria exist for some but not always strictly health based
Disease burden	Often unknown and seldom estimated partly due to lack of data	Often estimated in terms of DALY, QALY, COI etc. based on data
Approach of risk assessment	Bottom-up (from exposure to risk)	Bottom-up and top-down (from epidemiological data to risk)
Outcome of risk assessment	Safety (over or below or margin to a HBGV or similar)	Risk (probability of illness or number of cases)
Scope of risk assessment	Often no What-if scenarios evaluated	What-if scenarios important for evaluating management options

risk assessments have parallels in MRA, but additional features had been developed to account for the differences between chemicals and microbes (EPA 2012b, 2014)). Distinguishing features associated with microorganisms included growth and death; detection methodologies; genetic diversity and evolution of pathogens; host immunity and susceptibility; a wide dose range due to inter- and intra-species (strain) variation resulting in a great diversity in health end-points for different hosts, species, strains and over time; secondary (human-to-human) transmission; more heterogeneous spatial and temporary distribution; and zoonotic potential (ability of some pathogens to amplify in animals which then may act as sources of contamination and illness) (EPA 2014). The main, general (true for most but not all), differences and commonalities between chemical and biological hazards are summarized in this section (Table 1). These differences, as well as traditions, contribute to different approaches being used in CRA and MRA. Recent developments, *e.g.* iRisk (Chen et al. 2013) have adopted approaches which enable a greater commonality working with both classes of hazards for instance by addressing both in the same tool, and using a common risk metric.

Detection methodologies

In contrast to methods for detection of pathogens in food and water, chemical methods can generally quantify concentrations well below levels known to cause human health effects. Theoretically, a single infectious pathogenic microorganism may colonize a host and cause symptoms. Microbiological analytical methods for detecting levels corresponding to a single microorganism are often not available. Also, viable and non-viable micro-organisms may not always be distinguished and the detection outcome is always specific on the sampling and analysis time and location. The interpretation of non-detects when estimating concentration distributions may differ where chemicals usually are assumed to be left-censored whereas for microorganisms this may be the assumption or not in the estimation model.

Acute vs. lifetime effects

Most interest in relation to chemical hazards is directed towards health effects that have a long latency period before progressing to more severe adverse effects over time as result of low chronic exposure doses. In contrast, most interest for microbiological hazards has been directed at acute effects. However, acute and long-term effects/sequelae may be relevant for both types of hazards (Fink-Grernmels 1999; Pitt 2000; Keithlin et al. 2014) but the short-term (symptomatic or asymptomatic) infection is always a prerequisite for long-term effects caused by microorganisms.

Continuous vs. case based effects

Another important difference is that in CRA the potential critical health effect may be continuous and not binary in terms of outcome, *i.e.* the endpoint is not a case of illness.

For example a change in body or organ weights in experimental animals, which historically have been common critical effects (Sand et al. 2018). Such data on continuous effects do not reflect a discrete case of illness and is therefore difficult to translate into measures of disease burden.

Attribution of health effect to hazard

Information on specific incidences of adverse health effects will rarely be available for chemical hazards since potential disease outcomes develop over long times and are often chronic in nature and may have multiple etiological factors. Thus, the contribution of a particular chemical hazard to the overall disease burden may not be easily determined, and is less straightforward than for microbial hazards. Hazard identification, characterization and exposure assessment that can be supported by clinical data and case studies facilitate the establishment of a causative link to the food chain. The latter type of data allows a top-down approach (from number of human cases to risk) to epidemiological risk estimation in addition to the bottom-up (from exposure to risk) predictive approach.

Exposure assessment

Microorganism numbers can change several orders of magnitude along the food chain depending on food handling and storage conditions whereas the potential change in chemical concentration along the food chain is generally smaller. For this reason, exposure assessment in MRA often requires a multi-step analysis employing modeling to provide estimates on microbial contamination at the level of consumption, although data on concentration and levels of microorganisms may be available at earlier stages in the food chain. Methods in predictive microbiology are generally used to predict changes in microorganism numbers under conditions in food. Direct measurements for microbes in foods may even be infeasible due to large samples needed to detect rare occurrences. Changes in chemical concentration, *e.g.* as a result of processing or food preparation prior to consumption, may also occur but this issue is not addressed in CRA at the same level of detail as in MRA. For risk assessment of pesticides it can, however, be noted that processing factors may be used, *e.g.* Scholz et al. (2018).

Dose-response models

With the notable exception of genotoxic carcinogens most of the chemicals are generally assumed to have thresholds. In practice, however, the same types of (sigmoidal) dose-response models are used descriptively for all groups of chemicals as part of the hazard characterization and derivation of the RP. CRA differs between compounds with respect to what is done after derivation of the RP. Dose-response modeling in MRA generally uses non-threshold models (a single pathogen can cause infection) for infectious microorganisms and threshold or probability of toxin production for toxin-producing microorganisms (*e.g. Cl. botulinum*). Microbial dose-response modeling has been reviewed (WHO/FAO 2003). In contrast to CRA, assessment factors are generally not employed in MRA even when models are based on animal data or on specific population subgroups but are considered as a source of uncertainty (*e.g.* (FDA/FSIS 2003)). In one approach to address the potential limitation of using animal data, the shape of the *Listeria monocytogenes* dose response curve was based on animal data whereas the location of the curve along the dose-range was anchored based on human mortality data (FDA/FSIS 2003). Another approach employed for *L. monocytogenes* was to estimate the model parameter r, the probability of infection if exposed to one bacterium, in an exponential dose-response model, by finding the values that when combined with extensive exposure assessments predicted the reported number of human cases in the whole population or in sub-populations defined by age or susceptibility (WHO/FAO 2004). Recent developments also include approaches to account for variability in pathogen virulence and susceptibility of different human populations and how it can be characterized in terms of the r-parameter (Pouillot et al. 2015). The two main differences between chemical and microbiological dose response modeling is the exposure time in the experiment and the lower dose limit. Dose response data typically represent lifetime exposures for chemical and one-time exposures for microbiological hazards, respectively. Further, conceptually there is a lower dose limit for microbial hazards, namely one cell. In practice, and assuming that cells are distributed according to a Poisson distribution, it is not possible to prepare defined doses with less than 10 cells in a serving. For human volunteer studies, given the probability of illness per microorganism and the number of individuals available for studies higher doses are usually required to be evaluated. The consequence, as for chemical hazards, is that it is necessary to extrapolate the dose-response curve into the low dose region. The recommendation of the WHO/FAO is to use microbiological dose-response models that are linear in the low-dose range (WHO/FAO 2003). Linear low-dose extrapolation in the case of carcinogenic substances has been accepted by the scientific community and is a suggested strategy in the US EPA cancer risk guidelines (EPA 2005). However, Jakobsen et al. (2016) estimated the dietary burden of acrylamide expressed as HALYs using two different low dose linear extrapolation methods for which results varied by a factor of five. For chemical hazards estimation of benchmark doses associated with responses below 5 or 10% are not recommended to avoid extrapolation below the range of the experimental doses in which case results may be quite model dependent. For derivation of a RP using the BMD method benchmark response (BMR) levels of 5 or 10% are therefore used as standards to define the BMD (EFSA 2009a), *i.e.* the starting point for further risk assessment by application of assessment factors or low-dose linear extrapolation. Lower BMRs (*e.g.*, 1%) have been applied for human epidemiological data since such response levels, in this case, have been regarded to be in the observable region (*e.g.*, EFSA 2009b) – so far default recommendations on the BMR have been exclusively based on experimental data. While the BMR ideally may be

determined to represent a non-adverse level of change in response of the given health effect, default values (5–10%) are used in practice (Sand, Portier and Krewski 2011; Hardy et al. 2017)). It may be noted that the BMD method adopts a risk conservative approach and addresses data quality by considering the lower confidence bound on the BMD as the RP, rather than the BMD point estimate.

Risk assessment vs. safety assessment

The assessments considered fit for purpose in CRA and MRA are fundamentally different. In CRA, if exposure assessment is lower or higher than the corresponding HBGV, the situation related to the chemical substances are considered to be of no or potential concern, respectively. For compounds that are both genotoxic and carcinogenic EFSA recommends a margin of exposure (MOE) [MOE = RP/exposure] of 10,000 or higher Thus in CRA the estimated exposure is usually compared, in one way or another, with a HBGV, RP or similar. Therefore, CRA relates in most cases to safety assessments rather than risk assessments, since a margin between the current exposure and some guideline value intends to ensure the absence of adverse effects rather than an estimate of the probability or degree of response under the current exposure. In contrast, MRA aims to calculate the probability of illness based on the current exposure and estimates the consequences in terms of the selected end-point of the dose-response model with any biases associated with the data, assumptions and models.

Treatment of variability and uncertainty

There are numerous sources of variability and uncertainty in both CRA and MRA, and this has increasingly been acknowledged by development of stochastic modeling in the assessments. In general, variability and uncertainty is commonly addressed by stochastic modeling in MRA. Stochastic methods that account for both variability and uncertainty have also been developed in CRA (WHO/IPCS 2014), but practical risk assessments are often deterministic. For example, exposure assessments by EFSA account for variability in consumption patterns, by evaluating results associated with specific percentiles of exposure (point estimates), but so far with limited consideration of uncertainty although this may change with new proposed guidelines (Benford et al. 2018). In both CRA and MRA, there is a general lack of consumption data to account for variability in usual, chronic exposures between individuals, in acute exposures between days or servings, and the dependency between consumption of different food items and their handling. For assessment of chronic exposure to chemicals, mean concentrations in different foods are generally used as a basis, since this may best reflect long-term lifetime exposure. Similar to MRA a range of concentration values would, however, be used for acute assessments.

Main issues to address when comparing chemical and microbiological risk

Items to be ranked can include combinations of one hazard-one food, one hazard-multiple foods, one food-multiple hazards, or multiple hazards-multiple foods. Several major food safety agencies have issued work on the methods and tools used for ranking. For instance, a conceptual risk ranking framework for microbial hazard-food combinations has been suggested by EFSA (2012b), and this framework was later used for the development of a risk ranking toolbox (EFSA 2015b). Critical steps that define the final ranking outcome include definitions of what is to be ranked, selection of risk metrics, ranking approach, model types and model variables. A review on the methods for risk ranking including also chemicals and nutrition (van der Fels-Klerx et al. 2015), classified methods into eleven categories based on their characteristics such as modeling type (comparative risk assessment, risk ratio, scoring methods, risk matrices, multi criteria decision analysis) and risk metrics (cost of illness, health adjusted life years). The simultaneous assessment of more than one class of hazard offers in some ways similar challenges as the combined assessment of both risk and benefits. Risk and benefit analysis in different domains have been the subject of some research projects, *e.g.* BEPRARIBEAN (Verhagen et al. 2012), Brafo (Hoekstra et al. 2012). The experiences from the BEPRARIBEAN project of risk-benefit analysis in the different domains; Medicines, Food Microbiology, Environmental Health, Economics & Marketing-Finance and Consumer Perception, were summarized into a list on how to advance integrated risk-benefit analysis of food and nutrition (Tijhuis et al. 2012). It can be observed that many of the areas proposed were not in the risk/benefit assessment domain but rather associated to communication and management components. One of the assessment-related proposals was to integrate risk and benefits from many domains to achieve a greater applicability and practical use of assessment results. This reasoning, if transferred to the context of the present article, may be interpreted as advocating for a need to address chemical and microbiological hazards in a common framework to allow risk ranking across these classes of hazards.

Simultaneous comparisons of both chemical and microbiological risks require a common metric for both classes of hazards. Different HALY metrics, *e.g.* Disability Adjusted Life Years (DALY) (Havelaar et al. 2015), or economic measures such as cost of illness (COI), Willingness to pay (WTP) can be used. These measures often give different rankings of hazards. This reflects their emphasis on different components of the disease burden and illustrates the impact that the choice of metrics may have on ranking (Mangen et al. 2015). DALY addresses the impact of exposure to a specific hazard and the resulting different health endpoints associated with potentially different severities in an integrated measure of the disease burden. The burden is expressed as the total years lost in a population due to premature deaths and time lived with disabilities (Lopez et al. 2006). While the use of DALYs for microbiological hazards is well established, DALYs are not up to now a common

metric in CRA due to the poorly defined chronic effects of exposure since the use of DALYs requires estimation of quantitative effects in the population.

A semi-quantitative approach for ranking of both pathogens and chemicals in food employing HALYs was suggested by Newsome et al. (2009). This framework was later developed by US FDA into FDA-iRisk, a web based risk assessment system. This system allows simultaneous comparisons of hazard-food pairs and ranking of risks coming from both chemical and microbiological hazards for acute and chronic (chemical) effects in single or multiple foods based on Monte Carlo simulation (Chen et al. 2013). The tool is based on standard data entry templates for seven components: the food; the hazard; the population of consumers; process models describing the occurrence and amounts of the hazard up to the time of consumption; consumption patterns; dose-response curves; and health effects. Based on data and assumptions, the mean risk of illness and disease metrics, such as number of cases and DALYs is estimated. Users can choose from a range of default models and distributions but can also add and model their own data, *e.g.* dose response curve with alternative mathematical models. However, the parameters in the seven components have to be supplied by the user, *e.g.* for the distributions and dose-response models. The tool offers the ability to use functions to evaluate variability and uncertainty, carry out sensitivity analysis and compute changes in hazard concentration due to physical processes such as partitioning and mixing. For comparisons and ranking the chronic effects are scaled down to a per year basis based on the average lifetime used in the assessment. To be able to compute DALYs, QALYs, Cost of illness (COI) for the specific health endpoints, the estimate per case must be supplied by the user. The dose-response models describe the probability of an effect for different doses and if the endpoint does not represent or is equivalent to a frank case of illness, a possibility would be to scale this endpoint to represent a fraction of a case value, between 0 and 1. This can potentially be seen as a mechanism to translate non-case based effects, *e.g.* weight of a body organ, enzyme levels into cases. The final assessment and ranking of hazards is based on the estimates of disease burden in terms of DALYs or QALYs or COIs. Another government initiative to compare chemical, microbiological and nutritional hazards include the Our Food Our Health report from the Netherlands (van Kreijl, Knaap and Van Raaij 2006). The report estimated, based mostly on epidemiological data, the DALÝs associated with different hazards.

Introducing the case studies

Case studies were carried out to identify main issues to address when comparing chemical and microbiological risks. It is emphasized that the hazard-food combinations are selected based on the convenient availability of data. It is the comparison between approaches and the resulting outcomes in terms of rank order that are of interest, not the rankings as such, since these studies represent different geographic areas, populations and time periods. Two microbial hazard-food and chemical hazard-food combinations, respectively, were developed in the case studies to estimate the risk and subsequent ranking using either a chemical or a microbiological risk assessment approach. The microbiological case studies were: (i) The risk in elderly men (>75 years old) in the EU associated with Listeria monocytogenes and consumption of seven categories of ready to eat foods using dose-response models and data from Ricci et al. (2018). (ii) The risk associated with Salmonella in undercooked broiler for the general population in no specified geographic area, using dose-response models and data from WHO/FAO (2002). The chemical case studies were: (iii) The cancer risk associated with total dietary acrylamide exposure, and (iv) the risk of chronic kidney disease, defined as a globular filtration rate, GFR, below 60 mL/1.73 m^2 body surface/min, the critical effect used by Efsa (2010), associated with total dietary exposure to lead. The data used in the case studies are detailed in Table 2.

The chemical approach consisted of using BMDs corresponding to a 10% increased, added (lifetime) probability of a health effect. The margin of exposure, MOE, here defined as the ratio between the BMD_{10} (point estimate) and the estimated current mean exposures, was then calculated. BMD_{10} values are sometimes adjusted by assessment/uncertainty factors, for instance due to uncertainties associated with the extrapolation of dose response data for an animal species to humans. This was not done in the present study. Animal data is used for the acrylamide dose-response curve but extrapolation to humans is in this case considered part of the unquantified uncertainty of the assessments. The BMDs for the chemicals were determined from the dose-response data described in Table 2, as the dose corresponding to a 10% effect. The BMDs for the microorganisms were calculated from Equations (1)–(4) (shown with the listeria dose-response model as the example) as per RTE serving dose (assuming all RTE servings considered are contaminated with the dose 'BMD_{10}') corresponding to a lifetime (70 years) probability of at least one illness of 10% (Table 2). Illnesses from exposures (servings) were assumed independent events. Since the illness is rare, multiple infections per person are still rare.

$$P_{lifetime\ \ illness} = 0.1 = 1 - (1 - P_{illness\ \ per\ \ serving})^{70\ \times annual\ \ servings} \quad (1)$$

From Eq.1 $P_{\text{illness per serving}}$ is solved as

$$P_{illness\ \ per\ \ serving} = 1 - 0.9^{1/(70\ \times annual\ \ servings)} \quad (2)$$

Based on dose-response literature (Table 2), per serving probability is also written as a function of the dose 'BMD_{10}'

$$P_{illness\ \ per\ \ serving} = 1 - e^{-BMD_{10}\ *\ 2.9\times10^{-14}} \quad (3)$$

Then, BMD_{10} is solved from Eq. (2) and Eq. (3) as

$$BMD_{10} = -\log(0.9)/(70 \times annual\ \ servings \times 2.9 \times 10^{-14}) \quad (4)$$

where annual servings is the reported total number of servings per year of the RTE food categories considered in Ricci

Table 2. Data and literature sources used in the case studies.

Case study	Parameter	Value	Source/comment
Listeria-RTE food	Probability of illness per serving	$P_{ill} = 3.31 \times 10^{-8}$	(Ricci et al. 2018)
	Dose-response (DR)	$P = 1 - e^{-dose*2.9\times10^{-14}}$	(Ricci et al. 2018)
	DR end point (Health effect)	Severe illness (*e.g.* sepsis, meningitis)	(Ricci et al. 2018)
	Annual servings	417	(Ricci et al. 2018)
	Assessment factor to adjust DR	1	Assumption current paper
	BMD_{10} (log10 CFU)	8.10	Estimated current paper (Eq.4)
	Current mean exposure (log10 CFU)	$\log(1 - 3.31 \times 10^{-8})/(-2.9 \times 10^{-14}) =$ 1141379, *i.e.* 6.06 log10 CFU	Estimated from P_{ill} and P defined above
	DALY per case (including mortality)	0.60	(Mangen et al. 2015)
Salmonella –broilers	Probability of illness per serving	$P_{ill} = 1.13 \times 10^{-5}$	(WHO/FAO 2002)
	Dose-response	$P = 1 - (1 + \frac{dose}{51.45})^{-0.1324}$	(WHO/FAO 2002)
	DR end point (Health effect)	Gastrointestinal symptoms	(WHO/FAO 2002)
	Annual servings	26	(WHO/FAO 2002)
	Assessment factor to adjust DR	1	Assumption current paper
	BMD_{10} (log10 CFU)	−1.64	Estimated current paper
	Current mean exposure (log10 CFU)	−2.36	Estimated current paper
	DALY per case (including sequelae and mortality)	0.046	(WHO/FAO 2002)
Acylamide - food	BMD_{10} (μg/kg/day)	384	BMD associated with additional risk of 10% according to log-logistic model using data in (EFSA 2015a)
	DR endpoint (Health effect)	Cancer	(EFSA 2015a)
	Assessment factor to adjust DR	1	Animal data used but no AF used for extrapolation to "average" human
	Mean exposure (μg/kg/day)	0.5	(EFSA 2015a)
	DALY per case (including cancer illness and mortality)	6.7	(Pennington et al. 2002)
Lead - food	BMD_{10} (μg/kg/day)	0.68	BMD_{10} = 16.3 μg/L (associated with additional risk of 10%) according to the log-logistic model using data in (EFSA 2010). This BMD has been converted to 0.68 μg/kg/day using the same approach as in (EFSA 2010)
	DR endpoint (Health effect)	Chronic kidney disease defined as a globular filtration rate, GFR, below 60mL/1.73 m^2 body surface/min.	(EFSA 2010)
	Assessment factor to adjust DR	1	Data on humans used
	Mean exposure (μg/kg/day)	0.5	(EFSA 2012a)
	DALY per case (including kidney damage)	0.67	(Pennington et al. 2002)

et al. (2018). The current mean exposure per RTE serving to the microorganism were calculated from the probability of illness, P_{ill}, reported in the literature sources using the dose-response relationships directly (Table 2). Baseline probability of illness caused by the microorganism via other than the investigated foods was not considered. Dose-response data for the microorganisms was from humans and no assessment factor was applied to the BMD_{10}.

The microbiological approach consisted of estimating the probability of illness per person and year based on the estimated current mean exposures and the corresponding dose response curves (chemical hazards) or directly using the probabilities of illness reported in the literature sources (microbiological hazards) (Table 2). The latter have been estimated based on data on the prevalence of contaminated servings whereas the data on exposure to chemicals were based on the average exposure over all servings. The probabilities of illness were adjusted and expressed as the average probability of illness per person and year. For microorganisms, the average probability of illness per serving reported in the literature sources were converted to yearly probability based on the consumption frequency, *i.e.* using Equation (1) and the annual number of servings instead of lifetime number of servings (Table 2). For chemical hazards, the probability of a lifetime effect, given the estimated average exposure for adults within the EU, was divided by the lifetime, *i.e.* 70 years, to obtain the yearly risk. In addition, the yearly probability of illness per person was also calculated based on the estimated current exposures but using a linear extrapolation from the BMD_{10} down to zero instead of the actual dose response curves. This was done to investigate the sensitivity to this assumption since extrapolation into the low dose range may be sensitive to model choice. To address the impact of severity, the disease burden was calculated based on the estimated mean yearly risk per person and the reported DALY per case for microorganisms (Mangen et al. 2015) or the DALY per illness category reported for defined effect categories in Crettaz et al. (2002) for the chemical hazards.

Ranking using a chemical BMD/MOE approach or a microbial risk assessment approach

Based on the chemical approach, total dietary exposure of lead was associated with the lowest margin of exposure, followed (in increasing order of margin of exposure) by salmonella in broiler, listeria in ready to eat foods in elderly men, and lastly by acrylamide in food (Table 3). The same

Table 3. A summary of risk estimates and rankings from the case studies described in Table 2, using either a chemical or a microbiological risk assessment approach for ranking of four different hazard-food combinations.

	CRA		MRA - Probability				MRA - DALY			
Hazard-food combination	MOE	Rank	Mean probability of illness per person and year (DR-curve)[a]	Rank	Mean probability of illness per person and year (BMD_{10})[b]	Rank	DALY (mean μDALY per person and year)[a]	Rank	DALY (mean μDALY per person and year)[b]	Rank
Listeria – RTE food (men >75 years)	110	3	1.4×10^{-5}	3	1.4×10^{-5}	3	8	3	8	4
Salmonella-broiler	5	2	2.9×10^{-4}	2	2.9×10^{-4}	2	13	2	13	2
Lead - food	1.4	1	0.0011	1	0.0011	1	730	1	700	1
Acrylamide – food	770	4	2.9×10^{-7}	4	1.9×10^{-6}	4	2	4	12	3

[a]Based on estimated/calculated dose-response curve (DR).
[b]Based on linear extrapolation from BMD_{10} to zero.

rank order resulted when using the microbial risk assessment approach based directly on the dose response curves, with roughly the same absolute differences between hazards except for acrylamide. The differences in MOE varied a factor of 550 between highest and lowest, *i.e.* acrylamide and lead whereas the differences in probability of illness per year varied a factor of 3800 (Table 3). If an assessment factor would have been used for acrylamide due to the use of animal dose response data the MOE would have decreased a factor of 10 and changed the acrylamide rank from four to three. Ranking using a microbiological approach, but based on a linear extrapolation approach from the BMD_{10} down to zero instead of the actual dose-response curve did not affect the rank order, but did increase the estimated yearly acrylamide probability of illness (Table 3). The increased estimated risk of acrylamide when using linear low-dose extrapolation from the BMD_{10} instead of the full dose-response curve reflects that the former approach can be conservative, possibly overestimating probability. This is not a general observation since this was not the case for lead where the estimated probabilities were practically the same (Table 3). In contrast, the estimates for microbial hazards were the same independent of using the dose-response curve directly or low-dose extrapolation from the BMD (Table 3). This is a consequence of the dose-response curves used being linear in this dose range, which is in line with the recommendation of using single hit models (WHO/FAO 2003).

Rank order based on the MRA approach but also including severity, using DALY, resulted in essentially the same ranking order except when using the linear extrapolation method when acrylamide ranked in third and listeria in fourth place (Table 3). However, the absolute differences in DALY per person and year were small, less than a factor of seven between ranks two to four and a factor of 366 between ranks 1 to four, compared to using only the probabilities of a health effect (Table 3). This reflects the importance of the severity of the health effects being evaluated and emphasize the need for good DALY estimates. The DALY values for the chemical hazards were based on categorized default values (Crettaz et al. 2002), whereas for microbial hazards they were based on actual data applied to disease models describing health outcomes associated with the specific hazards (Mangen et al. 2015). In addition, ranking of lead was based on data describing a continuous variable, glomerular filtration rate, where observations below a cutoff value for the continuous response was defined as cases of illness (kidney disease) with an associated health effect of 0.67 DALY per case. These assumptions imply additional uncertainties in the risk ranking.

Discussion

The case studies illustrate that it is possible to estimate and rank chemical and microbiological hazard-food combinations based on average MOE or average yearly risk per person with traditional approaches from each domain. Although based only on few examples they indicate that rank order but not the differences in absolute measures is similar using either the CRA or MRA approach. This is interesting, especially if acknowledging that the uncertainties associated with the risk estimates may be significant. Including a measure of severity in the form of DALY affected the outcome more, in terms of reduced differences between hazards, than the separate CRA and MRA approaches based only on the probabilities of, or margins to, a health effect. However, there are limitations using either approach for ranking hazards from the chemical and the biological domain. The main limitations of applying the microbiological risk assessment approach is the extensive demand for data and resources, which is true for bottom up approaches in general. The main limitation of the chemical approach is that the outcome is not risk and case-based in the sense that it is not directly clear what a margin of exposure reflects in terms of disease burden. This is especially true since the severity of health effects is not generally considered. Sand et al. (2015) suggested the use of a specific assessment factor for the severity of the critical effect to estimate a severity-adjusted margin of exposure (Sand et al. 2015). This addresses severity within the current approach in a systematic manner but does not change the fundamental nature of the risk characterization metric used in CRA. In contrast, the microbiological approach may be translated into cases for any given population in order to estimate not only individual risk but also population risk which is an advantage/necessity for ranking. Importantly also for ranking, when data is given per case it is also possible to use DALY to address the effect of differences in severity between hazards.

Another limitation of the chemical risk assessment approach when applied to microorganisms is conceptual. In

the case studies (Table 2), the mean current exposures estimated from the reported current probability of illness and mean dose-response curves corresponded to millions of bacteria per serving (listeria) as well as to fractions of a cell per serving (salmonella). Neither estimates is representing reality and is partly a consequence of BMD not taking the concept of prevalence, *i.e.* the proportion of contaminated servings, into consideration. In addition, the case studies did not address variability in doses per serving or in susceptibility between individuals. Only mean doses and dose responses for the population of interest were used and this is a limitation especially for listeria where susceptibility may vary widely within risk groups (Pouillot et al. 2015). Thus, the mean exposure to bacteria per any serving is not a good estimate for exposure to microbial hazards since it does not reflect an actual scenario, in violation of validity concepts and good risk assessment practices (Burmaster and Anderson 1994; EPA 2000; Lammerding 2007; Fenner-Crisp and Dellarco 2016), and the effect of this on risk ranking is not clear. One potential solution may be to consider only servings contaminated with microorganisms. However, the impact of prevalence on ranking must then be addressed separately.

Other issues include differences between different time spans for exposure, per serving *vs.* lifetime, and acute *vs.* chronic health effects. These challenges should be possible to overcome conceptually by converting risk per serving to lifetime risk and evaluating the severities associated with the hazards, *e.g.* by the use of DALY. The main issue when assessing lifetime risk is how to apply this for children or age dependent risk groups, *e.g.* elderly, using constant consumption and dose-response models, since a scenario not happening in real life is assessed. In the case studies, life expectance was assumed to be 70 years to not include the childhood period but the problem remained in the listeria case study since elderly are not elderly for such a long time period.

A ranking based on risk rather than safety is desirable, as performed in the microbiological risk assessment approach. This approach is however resource intensive and is associated with difficulties when translating dose-response models based on animal data into absolute human risk, *e.g.* number of human cases. To support such efforts epidemiological data can assist (WHO/FAO 2004), and if wide discrepancies between approaches exist, *e.g.* as found in the estimates of the incidence of campylobacteriosis in the Netherlands based on epidemiology and QMRA, respectively, this is the starting point for further analysis (Bouwknegt et al. 2014). This is also a challenge for chemicals and top down CRA based on epidemiological data to anchor estimated cases to the observed cases are usually not available. One option to address any lack of data in risk assessment approaches would be to apply initial, screening level, risk assessments for ranking where default scenarios are being evaluated, but still including evaluation of potential effects of uncertainty and variability. It will still be a challenge to compare a case-based risk estimate with a non-case-based health-endpoint such as a biomarker or the filtration rate described in the lead example above. This is also related to the problem of integrating the severity of the health effect into ranking and the use of a common health metric of health burden such as DALY. One potential solution would be to define the continuous level as a percentage of a case, and thus, as a percentage of DALY per case, similar to what is done in iRisk for chemical hazards not frankly associated with a case (Chen et al. 2013). This is somewhat analogous to using one dose-response relationship for infection and one for illness for microorganisms, *e.g.* campylobacter dose-response (Teunis, Nagelkerke and Haas 1999). Sand et al. (2018) presents a method relating to this issue for chemicals. The method is based on a model (denoted "reference point profile") that describes the relation between the BMD for various effects (non-case-based as well as case-based effects), and the severity of toxicity determined for these effects. The concept can be generalized resulting in a description of the complete dose-response-severity volume. Outputs from the model, accounting for multiple effects, are weighted and summarized in units of a severe (case-based) outcome.

Concluding remarks

To achieve the goal of risk and science based management of foodborne hazards risk ranking based on the estimation of risk to human health is a first and important step. Prior to final ranking, uncertainties of the risk estimates also need to be taken into consideration. However, subsequent decisions on actions and priorities will be taken in a risk management context where rankings based on health risk will be one basis for decisions and where consideration of other legitimate factors such as economic costs and benefits, politics, trade, consumer views, also will be taken into account (Fazil et al. 2008). Thus, with the increasing demand for prioritization and holistic approaches for making decisions in relation to public health, sustainability and the environment, it would be useful to develop an approach that can address risk ranking of both chemical and microbiological hazards in food.

Risk assessments and ranking across hazard types has to be based on a common health metric, and, in line with the Codex risk analysis framework, preferably a HALY, *e.g.* DALY, rather than a monetary metric since economic costs are in the domain of risk management and other legitimate factors. As described in this article, there are many challenges associated with this task and several decisions have to be made to simplify the problem, but at the same time without losing the scientific soundness for the assessment and the ranking. Simplifications in the case of missing data or time constraints may be related to the level of detail of the assessment, *e.g.* screening level assessments, and the evaluation of a set of default (baseline) scenarios depending on the context. It can be argued that lifetime risk expressed as the yearly probability of a health effect is probably the best compromise to use for ranking across hazard types since it is easier, conceptually less problematic, to extrapolate from acute to lifetime exposures than from chronic to per serving exposures. As indicated in the case studies, the conversion

to yearly risk will be made differently for chemical and microbiological hazards, due to the differences between acute and chronic effects in relation to exposure. Health risks should be the basis for ranking without the inclusion of conservative management considerations. The uncertainty of the outcome based on the data, assumptions and models should be addressed as an integral part of the ranking. It is necessary to take severity into consideration, and in this context also be able to include data describing continuous, graded, effects and preferably convert (or translate) them into cases. One potential way forward would be to use separate approaches for the two classes of hazards or combinations of these two approaches, *i.e.* top down based on epi-data and attribution to pathways and food sources, and bottom-up approaches, respectively, while being aware of the biases this may introduce. The outcomes of assessments comparing both types of hazards would probably need to be a ranking based on disease burden, for example in terms of DALY, associated with the estimated number of cases, or proxy cases. Further work is required to explore which types of risk models or combinations of models and evidence that may best meet these requirements.

Disclosure statement

No potential conflict of interest was reported by the authors.

Disclaimer

This study is partly funded by Efsa but the views and opinions expressed in this article are those of the authors. They do not purport to reflect the opinions or views of Efsa.

Funding

This work was in part supported by the European Food Safety Agency (Efsa) under Grant GP/EFSA/AFSCO/2017/01. Dr. T. Langerholc was supported by Efsa under Grant GP/EFSA/AFSCO/2016/02, EU-FORA – The European Food Risk Assessment Fellowship program.

References

ANZFA. 2001. Food Safety: The priority classification system for food businesses: Australia New Zealand Food Authority, PO Box 7186, Canberra Mail Centre ACT. Australia, 2610.

Benford, D., T. Halldorsson, M. J. Jeger, H. K. Knutsen, S. More, H. Naegeli, H. Noteborn, C. Ockleford, A. Ricci, G. Rychen, et al. 2018. Guidance on Uncertainty Analysis in Scientific Assessments. *EFSA Journal* 16 (1):e05123. doi: 10.2903/j.efsa.2018.5123.

BfR. 2018. BfR risk communication in practice. German Federal Institute for Risk Assessment (Bundesinstitut für Risikobewertung, BfR.

Bouwknegt, M., A. B. Knol, J. P. van der Sluijs, and E. G. Evers. 2014. Uncertainty of population risk estimates for pathogens based on QMRA or epidemiology: A case study of Campylobacter in the Netherlands. *Risk Analysis* 34 (5):847–64. doi: 10.1111/risa.12153.

Buchanan, R. L., J. L. Smith, and W. Long. 2000. Microbial risk assessment: Dose-response relations and risk characterization. *International Journal of Food Microbiology* 58 (3):159–72. doi: 10.1016/S0168-1605(00)00270-1.

Burmaster, D. E., and P. D. Anderson. 1994. Principles of good practice for the use of Monte Carlo techniques in human health and ecological risk assessments. *Risk Analysis* 14 (4):477–81. doi: 10.1111/j.1539-6924.1994.tb00265.x.

Chen, Y. H., S. B. Dennis, E. Hartnett, G. Paoli, R. Pouillot, T. Ruthman, and M. Wilson. 2013. FDA-iRISK-A comparative risk assessment system for evaluating and ranking food-hazard pairs: Case studies on microbial hazards. *Journal of Food Protection* 76 (3): 376–85. doi: 10.4315/0362-028X.JFP-12-372.

CODEX. 2007. Working principles for risk analysis for food safety for application by governments. CAC/GL62-2007, Communication Division Electronic Publishing Policy and Support Branch, FAO, Rome, Italy.

Crettaz, P., D. Pennington, L. Rhomberg, K. Brand, and O. Jolliet. 2002. Assessing human health response in life cycle assessment using ED10s and DALYs: Part 1—Cancer effects. *Risk Analysis* 22 (5):931–46. doi: 10.1111/1539-6924.00262.

Crump, K. S. 1984. A new method for determining allowable daily intakes. Fundamental *and Applied Toxicology* 4 (5):854–71. doi: 10.1016/0272-0590(84)90107-6.

Dourson, M. L., R. C. Hertzberg, R. Hartung, and K. Blackburn. 1985. Novel methods for the estimation of acceptable daily intake. Toxicology *and Industrial Health* 1 (4):23–33. doi: 10.1177/074823378500100404.

European Food Safety Agency (EFSA). 2005. Opinion of the scientific committee on a request from EFSA related to a harmonised approach for risk assessment of substances which are both genotoxic and carcinogenic. *EFSA Journal* 3 (10):282. doi: 10.2903/j.efsa.2005.282.

European Food Safety Agency (EFSA). 2009a. Guidance of the Scientific Committee on Use of the benchmark dose approach in risk assessment. *EFSA Journal* 7 (6):1150. doi: 10.2903/j.efsa.2009.1150.

European Food Safety Agency (EFSA). 2009b. Scientific opinion on arsenic in food. EFSA panel on contaminants in the food chain (CONTAM). *EFSA Journal* 7 (10):1351. doi: 10.2903/j.efsa.2009.1351.

European Food Safety Agency (EFSA). 2010. Scientific opinion on Lead in Food. *EFSA Journal* 8 (4):1570. doi: 10.2903/j.efsa.2010.1570.

European Food Safety Agency (EFSA). 2012a. Lead dietary exposure in the European population. *EFSA Journal* 10 (7):2831. doi: 10.2903/j.efsa.2012.2831.

European Food Safety Agency (EFSA). 2012b. Scientific opinion on the development of a risk ranking framework on biological hazards. *EFSA Journal* 10 (6):2724–n/a. doi: 10.2903/j.efsa.2012.2724.

European Food Safety Agency (EFSA). 2015a. Scientific opinion on acrylamide in food. *EFSA Journal* 13 (6):4104. doi: 10.2903/j.efsa.2015.4104.

European Food Safety Agency (EFSA). 2015b. Scientific Opinion on the development of a risk ranking toolbox for the EFSA BIOHAZ Panel. *EFSA Journal* 13 (1):3939–n/a. doi: 10.2903/j.efsa.2015.3939.

EPA, U.S. 2000. *Risk characterization. Vol. EPA 100-B-00-002, U.S. Environmental Protection Agency Handbook*, Washington, DC, USA: Science Policy Council.

EPA, U.S. 2002. A review of the reference dose and reference concentration processes. EPA/630/P-02/002F. Risk Assessment Forum, U.S. Environmental Protection Agency.

EPA, U.S. 2005. Guidelines for carcinogen risk assessment. EPA/630/P-03/001F. Risk Assessment Forum, U.S. Environmental Protection Agency.

EPA, U.S. 2012a. Benchmark dose technical guidance. EPA/100/R-12/001. Risk Assessment Forum, U.S. Environmental Protection Agency.

EPA, U.S. 2012b. Microbial risk assessment guideline pathogenic microorganisms with focus on food and water. EPA/100/J12/001. U.S. Environmental Protection Agency.

EPA, U.S. 2014. Microbiological Risk Assessment (MRA) Tools, Methods, and Approaches for Water Media. EPA-820-R-14-009. Office of Water Office of Science and Technology, U.S. Environmental Protection Agency, Washington, DC 20460, USA.

FAO. 2011. Guidelines for risk categorization of food and food establishments applicable to ASEAN countries. RAP Publication 2011/22. Food and Agriculture Organization of the United Nations Regional Office for Asia and the Pacific.

FAO/WHO. 2006. Food safety risk analysis. A guide for national food safety authorities. FAO Food and Nutrition Paper 87.

FAO/WHO. 2009. Principles and methods for the risk assessment of chemicals in food. Environmental Health Criteria, 240, World Health Organization.

Fazil, A., A. Rajic, J. Sanchez, and S. McEwen. 2008. Choices, choices: The application of multi-criteria decision analysis to a food safety decision-making problem. *Journal of Food Protection* 71 (11): 2323–33. doi: 10.4315/0362-028X-71.11.2323.

FDA/FSIS. 2003. Quantitative assessment of relative risk to public health from foodborne listeria monocytogenes among selected categories of ready-tot-eat foods. Food and Drug Administration Center for Food Safety and Applied Nutrition, U.S. Department of Health and Human Services, Food Safety and Inspection Service, U.S. Department of Agriculture.

Fenner-Crisp, P. A., and V. L. Dellarco. 2016. Key elements for judging the quality of a risk assessment. *Environmental Health Perspectives* 124 (8):1127–35. doi: 10.1289/ehp.1510483.

Fink-Grernmels, J. 1999. Mycotoxins: Their implications for human and animal health AU – Fink-Grernmels, Johanna. *Veterinary Quarterly* 21 (4):115–20. doi: 10.1080/01652176.1999.9695005.

Gahan, C. G. M., and C. Hill. 2014. Listeria monocytogenes: Survival and adaptation in the gastrointestinal tract. *Frontiers in Cellular and Infection Microbiology* 4:9. doi: 10.3389/fcimb.2014.00009.

Hardy, A., D. Benford, T. Halldorsson, M. J. Jeger, K. H. Knutsen, S. More, A. Mortensen, H. Naegeli, H. Noteborn, C. Ockleford, et al. 2017. Update: Use of the benchmark dose approach in risk assessment. *EFSA Journal* 15 (1):e04658. doi: 10.2903/j.efsa.2017.4658.

Havelaar, A. H., M. D. Kirk, P. R. Torgerson, H. J. Gibb, T. Hald, R.J. Lake, N. Praet, D.C. Bellinger, N.R. de Silva, N. Gargouri, et al. 2015. World Health Organization global estimates and regional comparisons of the burden of foodborne disease in 2010. *PLoS Medicine* 12 (12):e1001923–e1001923. doi: 10.1371/journal.pmed.1001923.

Hoekstra, J., A. Hart, A. Boobis, E. Claupein, A. Cockburn, A. Hunt, I. Knudsen, D. Richardson, B. Schilter, K. Schütte, et al. 2012. BRAFO tiered approach for benefit–risk assessment of foods. *Food and Chemical Toxicology* 50:S684–S698. doi: 10.1016/j.fct.2010.05.049.

Jakobsen, L. S., K. Granby, V. K. Knudsen, M. Nauta, S. M. Pires, and M. Poulsen. 2016. Burden of disease of dietary exposure to acrylamide in Denmark. *Food and Chemical Toxicology* 90:151–9. doi: 10.1016/j.fct.2016.01.021.

Keithlin, J., J. Sargeant, M. K. Thomas, and A. Fazil. 2014. Systematic review and meta-analysis of the proportion of Campylobacter cases that develop chronic sequelae. *BMC Public Health* 14 (1):1203–1203. doi: 10.1186/1471-2458-14-1203.

Lammerding, A. M. 2007. Using Microbiological Risk Assessment (MRA) in Food Safety Management. Summary report of a workshop held in October 2005 in Prague, Czech Republic. ILSI Europe Report Series, ISBN 90-78637-05-9.

Lammerding, A. M., and A. Fazil. 2000. Hazard identification and exposure assessment for microbial food safety risk assessment. *International Journal of Food Microbiology* 58 (3):147–157. doi: 10.1016/S0168-1605(00)00269-5.

Lopez, A. D., C. D. Mathers, M. Ezzati, D. T. Jamison, and C. J. L. Murray. 2006. Measuring the global burden of disease and risk factors, 1990–2001. In *Global burden of disease and risk factors*, eds. Alan D. Lopez, Colin D. Mathers, Majid Ezzati, Dean T. Jamison and Christopher J. L. Murray, 1–14. Washington (DC): The International Bank for Reconstruction and Development/The World Bank; New York: Oxford University Press.

Mangen, M.-J. J., M. Bouwknegt, I. H. M. Friesema, J. A. Haagsma, L. M. Kortbeek, L. Tariq, M. Wilson, W. van Pelt, and A. H. Havelaar. 2015. Cost-of-illness and disease burden of food-related pathogens in the Netherlands, 2011. *International Journal of Food Microbiology* 196:84–93. doi: 10.1016/j.ijfoodmicro.2014.11.022.

McMeekin, T. A., and T. Ross. 2002. Predictive microbiology: Providing a knowledge-based framework for change management. *International Journal of Food Microbiology* 78 (1–2):133–153. doi: 10.1016/S0168-1605(02)00231-3.

Nauta, M. J. 2001. A modular process risk model structure for quantitative microbiological risk assessment and its application in an exposure assessment of Bacillus cereus in a REPFED. Report 149106 007 RIVM, Bilthoven. http://www.rivm.nl/bibliotheek/rapporten/149106007.pdf

Newsome, R., N. Tran, G. M. Paoli, L. A. Jaykus, B. Tompkin, M. Miliotis, T. Ruthman, E. Hartnett, F. F. Busta, B. Petersen., et al, 2009. Development of a risk-ranking framework to evaluate potential high-threat microorganisms, toxins, and chemicals in food. *Journal of Food Science* 74 (2):R39–45. doi: 10.1111/j.1750-3841.2008.01042.x.

Pennington, D., P. Crettaz, A. Tauxe, L. Rhomberg, K. Brand, and O. Jolliet. 2002. Assessing human health response in life cycle assessment using ED10s and DALYs: Part 2 - Noncancer effects. *Risk Analysis* 22 (5):947–963. doi: 10.1111/1539-6924.00263.

Pires, S. M. 2013. Assessing the applicability of currently available methods for attributing foodborne disease to sources, including food and food commodities. *Foodborne Pathogens and Disease* 10 (3): 206–213. doi: 10.1089/fpd.2012.1134.

Pitt, J. I. 2000. Toxigenic fungi and mycotoxins. *British Medical Bulletin* 56 (1):184–192. doi: 10.1258/0007142001902888.

Pouillot, R., K. Hoelzer, Y. Chen, and S. B. Dennis. 2015. Listeria monocytogenes dose response revisited—Incorporating adjustments for variability in strain virulence and host susceptibility. *Risk Analysis* 35 (1):90–108. doi: 10.1111/risa.12235.

Ricci, A., A. Allende, D. Bolton, M. Chemaly, R. Davies, P. S. Fernández Escámez, R. Girones, L. Herman, K. Koutsoumanis, B. Nørrung, et al. 2018. Listeria monocytogenes contamination of ready-to-eat foods and the risk for human health in the EU. *EFSA Journal* 16 (1): e0:5134. doi: 10.2903/j.efsa.2018.5134.

Sand, S., S. Bjerselius, L. Busk, H. Eneroth, J. Sanner Färnstrand, and R. Lindqvist. 2015. "The risk thermometer – A tool for risk comparison." National Food Agency (Livsmedelsverket) home page (2017-11-09): https://www.livsmedelsverket.se/globalassets/rapporter/2015/the-risk-thermometer.pdfRapport 8-2015.

Sand, S., R. Lindqvist, D. von Rosen, and N.-G. Ilbäck. 2018. Dose-related severity sequence, and risk-based integration, of chemically induced health effects. *Toxicological Sciences* 165 (1):74–89. doi: 10.1093/toxsci/kfy124.

Sand, S., C. J. Portier, and D. Krewski. 2011. A signal-to-noise crossover dose as the point of departure for health risk assessment. Environmental *Health Perspectives* 119 (12):1766–74. doi: 10.1289/ehp.1003327.

Scholz, R., M. Herrmann, A. Kittelmann, M. von Schledorn, G. van Donkersgoed, C. Graven, T. van der Velde-Koerts, C. Anagnostopoulos, E. Bempelou, and B. Michalski. 2018. Database of processing techniques and processing factors compatible with the EFSA food classification and description system FoodEx 2 Objective 1: Compendium of Representative Processing Techniques investigated in regulatory studies for pesticides. *EFSA Supporting Publications* 15 (11):1508E. doi: 10.2903/sp.efsa.2018.EN-1508.

Stafford, R. J., P. J. Schluter, A. J. Wilson, M. D. Kirk, G. Hall, L. Unicomb, and Group OzFoodNet Working. 2008. Population-attributable risk estimates for risk factors associated with Campylobacter infection, australia. *Emerging Infectious Diseases* 14 (6):895–901. doi: 10.3201/eid1406.071008.

Teunis, P. F. M., N. J. D. Nagelkerke, and C. N. Haas. 1999. Dose response models for infectious gastroenteritis. *Risk Analysis* 19 (6):1251–1260. doi: 10.1111/j.1539-6924.1999.tb01143.x.

Tijhuis, M. J., M. V. Pohjola, H. Gunnlaugsdóttir, N. Kalogeras, O. Leino, J. M. Luteijn, S. H. Magnússon, G. Odekerken-Schröder, M. Poto, J. T. Tuomisto., et al, 2012. Looking beyond borders: Integrating best practices in benefit–risk analysis into the field of Food and Nutrition. *Food and Chemical Toxicology* 50 (1):77–93. doi: 10.1016/j.fct.2011.11.044.

Van der Fels-Klerx, H. J., E. D. Van Asselt, M. Raley, M. Poulsen, H. Korsgaard, L. Bredsdorff, M. Nauta, M. D'Agostino, D. Coles, H. J. P. Marvin, et al. 2018. Critical review of methods for risk ranking of food-related hazards, based on risks for human health. Critical *Reviews in Food Science and Nutrition* 58 (2):178–193. doi: 10.1080/10408398.2016.1141165.

van der Fels-Klerx, H. J., E. D. van Asselt, M. Raley, M. Poulsen, H. Korsgaard, L. Bredsdorff, M. Nauta, V. Flari, M. d'Agostino, D. Coles, et al. 2015. Critical review of methodology and application of risk ranking for prioritisation of food and feed related issues, on the basis of the size of anticipated health impact. *EFSA Supporting Publications* 12 (1)710E–n/a. doi: 10.2903/sp.efsa.2015.EN-710.

Van Der Voet, H., and W. Slob. 2007. Integration of probabilistic exposure assessment and probabilistic hazard characterization. *Risk Analysis* 27 (2):351–371. doi: 10.1111/j.1539-6924.2007.00887.x.

van Kreijl, C. F., A. G. A. C. Knaap, and J. M. A. Van Raaij. 2006. Our food, our health-Healthy diet and safe food in the Netherlands. RIVM report number 270555009. National Institute for Public Health and the Environment and 3720 BA Bilthoven P.O. Box 1, The Netherlands.

van Lier, A., S. A. McDonald, M. Bouwknegt, M. E. Kretzschmar, A. H. Havelaar, M-J J. Mangen, J. Wallinga, and H. E. de Melker. 2016. Disease burden of 32 infectious diseases in the Netherlands, 2007-2011. *PloS One* 11 (4):e0153106. doi: 10.1371/journal.pone.0153106.

Verhagen, H., M. J. Tijhuis, H. Gunnlaugsdó ttir, N. Kalogeras, O. Leino, J. M. Luteijn, S. H. Magnússon, G. Odekerken, M. V. Pohjola, J. T. Tuomisto, et al. 2012. State of the art in benefit–risk analysis: Introduction. *Food and Chemical Toxicology* 50 (1):2–4. doi: 10.1016/j.fct.2011.06.007.

WHO. 2015. WHO estimates of the global burden of foodborne diseases, Edited by World Health Organization. Geneva, Switzerland: WHO publications.

WHO/FAO. 2002. Risk assessments of Salmonella in eggs and broiler chickens, Vol. 2, Microbiological risk assessment series: Food & Agriculture Org.

WHO/FAO. 2003. Hazard characterization for pathogens in food and water, Guidelines, Microbiological Risk Assessment Series: Food Safety Department, World Health Organization, Geneva, Switzerland.

WHO/FAO. 2004. Risk assessment of Listeria monocytogenes in ready-to-eat foods: technical report. Vol. 5, Microbiological risk assessment series: Food Safety Department, World Health Organization, Geneva, Switzerland.

WHO/IPCS. 1994. Assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits. World Health Organization, International Programme on Chemical Safety

WHO/IPCS. 2014. Guidance document on evaluating and expressing uncertainty in hazard characterization. 11. World Health Organization, International Programme on Chemical Safety