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Review

The role of hazard- and risk-based approaches in ensuring food safety

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ABSTRACT

Background: Food legislation in the European Union and elsewhere includes both hazard- and risk-based approaches for ensuring safety. In hazard-based approaches, simply the presence of a potentially harmful agent at a detectable level in food is used as a basis for legislation and/or risk management action. Risk-based approaches allow consideration of exposure in assessing whether there may be unacceptable risks to health.

Scope and approach: The advantages and disadvantages of hazard- and risk-based approaches for ensuring the safety of food chemicals, allergens, ingredients and microorganisms were explored at an ILSI Europe workshop.

Key findings and conclusions: It was concluded that both types of approach have their place, depending on the context. However, problems can arise when both types of approach are used in regulation by separate agencies that address different aspects of the same agent/substance present in food. This separation of decision-making can result in hazard-based restrictions on marketing and use, whereas risk-based assessments for those exposed show there is reasonable certainty no harm will result. This in turn can lead to contradictory, confusing and ultimately unnecessary actions. Use of hazard-based approaches for foods also means that comparisons with benefits for nutrition and food security cannot be undertaken. This has the potential to lead to bias in the overall conclusions of regulators and risk managers, who may not have been presented with the benefits of particular foods. The value of risk-based approaches is becoming increasingly recognised.

1. Introduction

Food safety is not absolute and in 1993 OECD prepared a working definition, namely "a reasonable certainty that no harm will result from intended uses under the anticipated conditions of consumption" (OECD, 1993). This definition recognises that zero tolerance of risks is not feasible for the majority of foods and the majority of safety contexts. In the field of food safety assessment, both hazard-based and risk-based approaches are used to ensure food safety. In hazard-based approaches, simply the presence of a potentially harmful agent at a detectable level in food is used as a basis for legislation and/or risk management action. Risk-based approaches, on the other hand, try to establish health-based guidance values for human exposure to chemicals, such as

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Nomenclature

BRAFO	Benefit and Risk Analysis for Foods (EU Project)
CFU	Colony Forming Unit
CLP	Classification, Labelling and Packaging
CMR	Carcinogenicity, Mutagenicity and toxicity to Reproduction
DPD	Dangerous Preparations Directive
DSD	Dangerous Substance Directive
EAACI	European Academy of Allergy and Clinical Immunology
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
EMA	European Medicines Agency
FAO	Food and Agricultural Organization of the United Nations
GHS	Globally Harmonized System of classification and labelling
GM	Genetically Modified
IPCS	International Programme on Chemical Safety
MLs	Maximum Levels
NOAEL	No-Observed-Adverse-Effect Level
OECD	Organisation for Economic Co-operation and Development
PBT	Persistent, Bioaccumulative and Toxic
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
SVHC	Substance of Very High Concern
vPvB	very Persistent and very Bioaccumulative
WHO	World Health Organization
WTO	World Trade Organization

acceptable or tolerable daily intakes, using toxicological data; estimates of human exposure are then compared with the health-based guidance value to assess whether there may be an unacceptable risk to health and whether risk management action is needed. In risk-based approaches for microbiological agents, it is not necessarily human exposure that is estimated, but the prevalence and concentration of the microorganism somewhere in the food chain, from which the size of the potential risk can be assessed and a judgement made as to whether it is acceptable.

Hazard- and risk-based approaches have a common element in that identification of the hazard is a first step in both. In hazard-based approaches, the hazard may then be characterised (see below for definitions). In risk-based approaches this will be followed by exposure assessment and the integration of exposure with hazard characterisation in the final risk characterisation step, in order to provide an overall risk assessment, from which to conclude on safety.

An ILSI Europe workshop in December 2014 entitled "Hazard vs. Risk Based Approaches in Food Safety Assessment" explored the use of both types of approach in various areas of food safety assessment, including chemical contaminants and residues, whole foods and novel foods, microbiological agents, and food allergens. This paper summarises the main issues discussed at the workshop. Although the focus here is on hazard- and risk-based approaches to ensure food safety in Europe, some of the arguments may also be relevant to safety assessment beyond Europe and also in other, non-food areas.

2. Definition of terms

It is important to distinguish between hazard (the intrinsic potential to cause harm), and risk (the probability of harm occurring at a given exposure), even though it appears from surveys that the public do not generally differentiate between these two terms (Ley, 1995; Scheer et al., 2014; Ulbig, Hertel, & Böl, 2010; Young, Brelsford, & Wogalter, 1990). It is also apparent that the terms 'hazard' and 'risk' are perceived and used very differently in risk communication depending on the perspective of the stakeholders, including differing use among risk assessment experts and between European Union (EU) Member States (Chakraborty, 2012; Scheer et al., 2014; Ulbig et al., 2010). In this paper, the following definitions are used. They have been developed mainly in relation to chemical hazard and risk assessment and are taken from IPCS (2004), except where otherwise stated. Some of the same terms are also used in relation to microbiological hazard and risk assessment, but the definitions can differ somewhat from those used for chemicals. The microbiological definitions can be found in Codex Alimentarius, 1999.

Hazard *Inherent property of an agent or situation having the potential to cause adverse effects when an organism, system, or (sub) population is exposed to that agent.*

Risk *The probability of an adverse effect in an organism, system, or (sub)population caused under specified circumstances by exposure to an agent.*

Risk assessment *A process intended to calculate or estimate the risk to a given target organism, system, or (sub)population, including the identification of attendant uncertainties, following exposure to a particular agent, taking into account the inherent characteristics of the agent of concern as well as the characteristics of the specific target system. The risk assessment process includes four steps: hazard identification, hazard characterization, exposure assessment, and risk characterization.*

Hazard assessment *A process designed to determine the possible adverse effects of an agent or situation to which an organism, system, or (sub)population could be exposed. The process includes hazard identification and hazard characterization. The process focuses on the hazard, in contrast to risk assessment, where exposure assessment is a distinct additional step.*

Hazard identification *The identification of the type and nature of adverse effects that an agent has an inherent capacity to cause in an organism, system, or (sub)population. Hazard identification is the first stage in hazard assessment and the first of four steps in risk assessment.*

Hazard characterisation *The qualitative and, wherever possible, quantitative description of the inherent property of an agent or situation having the potential to cause adverse effects. This should, where possible, include a dose–response assessment and its attendant uncertainties. Hazard characterization is the second stage in the process of hazard assessment and the second of four steps in risk assessment.*

Exposure assessment *Evaluation of the exposure of an organism, system, or (sub)population to an agent (and its derivatives). Exposure assessment is the third step in the process of risk assessment.*

Risk characterisation *The qualitative and, wherever possible, quantitative determination, including attendant uncertainties, of the probability of occurrence of known and potential adverse effects of an agent in a given organism, system, or (sub)population,*

under defined exposure conditions. Risk characterization is the fourth step in the risk assessment process.

Food security *Physical and economic access to food that meets people's dietary needs as well as their food preferences (definition from World Food Summit, 1996, see WHO website http://www.who.int/trade/glossary/story028/en/).*

Acceptable daily intake *Estimate of the amount of a chemical in food or drinking-water, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risk to the consumer (definition from IPCS, 2009).*

Tolerable daily intake *Analogous to Acceptable daily intake. The term "tolerable" is used for agents that are not deliberately added, such as contaminants in food.*

Mode of action *A biologically plausible sequence of key events leading to an observed effect supported by robust experimental observations and mechanistic data (definition from IPCS, 2009).*

Margin of exposure *Ratio of the no-observed-adverse-effect level (NOAEL) for the critical effect to the theoretical, predicted, or estimated exposure dose or concentration. (Note that points of departure other than the NOAEL may also be used.)*

No-Observed-Adverse-Effect Level (NOAEL) *Greatest concentration or amount of a substance, found by experiment or observation, that causes no adverse alteration of morphology, functional capacity, growth, development or lifespan of the target organism distinguishable from those observed in normal (control) organisms of the same species and strain under the same defined conditions of exposure (definition from IPCS, 2009).*

Precautionary principle *In specific circumstances where, following an assessment of available information, the possibility of harmful effects on health is identified but scientific uncertainty persists, provisional risk management measures necessary to ensure the high level of health protection chosen in the Community may be adopted, pending further scientific information for a more comprehensive risk assessment (EC, 2002).*

2.1. Public attitudes to risk

Public attitudes to risk are complex and are influenced by many factors (see, for example, Hansen, Holm, Frewer, Robinson, & Sandøe, 2003; EC, 2010; Ropeik, 2011; Scheer et al., 2014). Some commentators have suggested that Europe has become generally more risk averse and precautionary in recent years in the regulation of risks, compared with, for example, the United States of America (Laidi, 2010; Vogel, 2012). However, other researchers that have analysed legislative responses to a diverse range of risks, including food risks, conclude that, averaging over all risks, there is no significant difference in precaution between the two geographical areas and that within each area, there is a diversity of trends across risks with respect to precaution, with the most common being no change in relative precaution over time (Hammitt, Wiener, Swedlow, Kall, & Zhou, 2005; Wiener, Rogers, Hammitt & Sand, 2011).

In those individuals that are generally more risk averse with respect to exposure to chemicals, they may view chemicals as being 'not natural', as being of benefit to industry rather than to consumers, and that chemicals are overused and misused, resulting in human disease and environmental pollution. Consequently exposure to chemicals is seen as involuntary and of concern (Slovic & Weber, 2002; EC, 2009a; Callan & Thomas, 2013).

Consumer tolerance of risks is significantly influenced by awareness of the risk. For example, individuals with allergies have high awareness and are more likely to accept some risk. On the other hand, the sporadic nature of food poisoning and the fact that it is common results in low awareness of microbial risks, while most people are not aware whether chemical risks are important or not.

3. The current regulatory climate

In most countries around the world, the regulation of chemicals in general (not just those encountered in the food sector) includes a mix of both hazard-based and risk-based approaches. In Europe, there is currently a very active debate between EU Member States on whether chemical regulations, particularly those related to classification and labelling (see below), should be based on hazard or on risk (Lofstedt, 2011).

In the EU, the mix of approaches can be seen, for example, in the legislation relating to the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), coordinated by the European Chemicals Agency (ECHA), which is partly hazard-based and partly risk-based. An essential aspect of REACH, which also impacts on some food chemicals, is the regulation on classification, labelling and packaging (CLP) of substances and mixtures (EC, 2008), which is hazard-based. It is primarily intended to identify all physico-chemical, toxicological and ecotoxicological properties that may cause harm during normal handling and use. In the toxicological area, it applies to hazard-based classification for carcinogens, mutagens and reproductive toxicants. As the European Commission (EC) comments in its guidance on the CLP regulation,

> *"The classification of chemicals is to reflect the type and severity of the intrinsic hazards of a substance or mixture. It should not be confused with risk assessment which relates a given hazard to the actual exposure of humans and the environment to the substance or mixture displaying this hazard. Nevertheless, the common denominator for both classification and risk assessment is hazard identification and hazard assessment."* (ECHA, 2009).

If we consider, for example, plant protection products, under the CLP legislation active substances (pesticides), safeners and synergists in plant protection products may be classified for their intrinsic, hazardous properties. This includes the toxicological properties of carcinogenicity, mutagenicity and toxicity to reproduction (CMR). A CMR classification indicates that the substance or mixture has the potential to cause harm, but does not identify the circumstances (exposures) under which harm may actually be caused, i.e. the risk of harm. However, hazard classification of a substance in one or more of the CMR 1A or 1B categories automatically triggers certain legislative restrictions on its approval, manufacture, marketing and use, irrespective of the outcome of any risk assessment of those actually exposed, unless the exposure of humans under realistic proposed conditions of use can be shown to be negligible (EC, 2009b). To this group of toxicological hazard triggers for legislative restrictions, endocrine disrupting properties are also now added for plant protection products and biocides (EC, 2009b, 2012), although the specific criteria for determination of endocrine disrupting properties have not yet been agreed in the EU. The CLP aspects of the chemicals in plant protection products are decided by ECHA on a hazard basis, whereas the safety aspects of chemical residues in food from the use of pesticides on crops are decided by the EU Member States working with the European Food Safety Authority (EFSA), using a risk-based approach.

Similarly, the REACH criteria for identification of a substance or mixture as Persistent, Bioaccumulative and Toxic (PBT), or very

Persistent and very Bioaccumulative (vPvB), as laid down in Annex XIII of the REACH Regulation, are based on substance-specific intrinsic properties, i.e. they are hazard-based (EC, 2008; Norlander, Simon, & Pearson, 2010). However, in contrast to CMR classifications (see above), in which there is no consideration of risk-based aspects in the REACH process, in the case of PBT and vPvB substances, risk-based aspects such as exposure, risks and alternatives to the chemical are considered when deciding whether to add the substance to the Candidate List for Substances of Very High Concern (SVHCs) (Norlander et al., 2010). In the case of products containing PBT or vPvB substances, a threshold for the concentration of such substances in products is set, above which a product will be classified as PBT or vPvB (ECHA, 2014).

While pesticides and biocides are subject to the CLP regulation, other chemicals that are present in food, such as contaminants and deliberately added substances like food additives and flavourings or substances migrating into food from food packaging, do not fall under the CLP regulation and are assessed and regulated solely using risk-based approaches (with the exception of avoidable genotoxic substances – see later). Novel foods and genetically modified foods are currently assessed and regulated using risk-based approaches, whereas food allergens and microbiological agents are currently mostly assessed and regulated by hazard-based approaches.

In the current regulatory climate, in the absence of sufficient evidence on hazard or risk, the potential for application of the Precautionary Principle also has to be considered. In the EU, a decision on whether or not to invoke the Precautionary Principle is exercised where scientific information is insufficient, inconclusive, or uncertain and where there are indications that the possible effects on the environment, or human, animal or plant health may be potentially dangerous and inconsistent with the chosen level of protection (EC, 2000a).

4. Differences between safety assessment of food chemicals, food allergens, whole foods, ingredients, and pathogenic microorganisms

Differences have evolved in safety assessment approaches for food chemicals (occurring either as contaminants, residues, or deliberately added), food allergens, whole foods and ingredients, including novel and genetically modified foods, and pathogenic microorganisms in food. This is due mainly to inherent differences in their nature.

For chemicals in foods, the risks to health mostly depend on the duration, frequency and level of exposure (concentrations in relevant foods x amount of relevant foods consumed). Low-level exposures are often of no or negligible risk, with the likelihood of risk increasing as exposure increases and, consequently, thresholds for triggering of toxicological effects are exceeded. Hence, risk-based approaches are more commonly used. There are exceptions to this for chemicals, as will be discussed below under “Cases where hazard assessment is appropriate”.

Food allergens may trigger adverse reactions at relatively low exposures in sensitive individuals. Since the thresholds for elicitation of allergic reactions can be extremely low and it is difficult to establish the thresholds for each allergen that may be of importance, a hazard-based approach is usually taken, for instance in communicating possible unintended allergen presence due to cross-contact contamination. In this approach, the (possible) presence of an allergen is indicated by labelling so that those who know they are susceptible can avoid that food. However, precautionary labelling with “may contain…” can restrict food choice for allergic individuals unnecessarily. Hence, a risk-based approach has been developed (the VITAL project, see http://www.eu-vital.org/en/home.html), based on the establishment of reference doses elaborated from a safety objective or accepted risk level agreed upon by stakeholders (Allen et al., 2014; Taylor et al., 2014). Another initiative on food allergen risk assessment has been undertaken by ILSI Europe (Hattersley, Ward, Baka, & Crevel, 2014; Crevel et al., 2014a, b).

Risk assessment of pathogenic microorganisms in food has to take into account that microorganisms can grow (multiply) during food processing and storage, that they are often inactivated during processing and preparation (e.g. with heat treatment), and that cross contamination may occur. Exposure can only be assessed by the use of processing data and predictive models, based on prevalence and concentration data in the raw material or the food product some time before consumption. A single living cell may result in illness, because microorganisms may multiply in the gut. These features have a large impact on the methods applied for both exposure assessment and hazard characterisation, and for the terminology used in microbiological risk assessment. For example, in microbiological risk assessment, the agent itself (microorganism) is considered a hazard and a hazard-based approach is generally based only on hazard assessment, excluding consideration of exposure assessment. Control is called “hazard-based” when it is known to decrease prevalence and/or concentrations of the specific hazard of concern, but the impact on human health risk is unknown. It is called risk-based when risk assessment is applied to assess impact on the incidence of human illness (Codex Alimentarius, 2011).

4.1. Hazard-based approaches

4.1.1. Chemicals

Hazard-based regulation of industrial chemicals has been in use for many years (e.g. for flammable, explosive, and corrosive hazards) and has been extended to cover certain toxicological hazards. In the EU, hazard-based regulation was covered in the past by the Dangerous Substances Directive (DSD) and the Dangerous Preparations Directive (DPD) (EC, 1967; EC, 1999), and is now covered by their replacement, the CLP Regulation (EC, 2008). The CLP Regulation takes into account the Global Harmonization System on classification and labelling (GHS) that has been developed and implemented internationally as a non-legally binding agreement (UN, 2011) These types of legislation and agreement ensure that knowledge about hazards is more widely available, that criteria for hazard classification and communication of hazard information is more uniform internationally, and that information on hazards is passed to users so that chemicals can be transported, used and disposed of safely. For example, internationally recognisable pictograms and hazard statements (formerly called risk phrases under the DSD and DPD) have been introduced to enable quick identification of hazards on containers of chemicals.

Some chemicals are regarded as so inherently hazardous to human health or the environment that they have triggered internationally agreed moves to ban or severely restrict their import, export and use. This includes a number of persistent chemicals with adverse effects on the environment and/or human health, such a DDT, aldrin, lindane, polychlorinated biphenyls and perfluorinated compounds (UNEP, 2013). It also includes pesticides with very high acute toxicity, such as paraquat, and certain cholinesterase inhibiting compounds, which have not only caused deaths from suicide, but also many accidental deaths among exposed workers, particularly in developing countries, and, less commonly, deaths from food contamination (Kishi, 2002; IFCS, 2003; Idrovo, 2014). This history has led to a renewed call from the Food and Agricultural Organization of the United Nations (FAO), World Health

Organization (WHO) and the World Bank that highly hazardous pesticide products should not be available to small scale farmers who lack knowledge and the proper sprayers, protective gear and storage facilities to manage such products appropriately (FAO, 2013). Particular examples are organophosphates such as monocrotophos, methamidophos, phophamidon, parathion and methyl-parathion, which have all been listed under the 1998 Rotterdam Convention as severely hazardous pesticide formulations and are subject to the agreed prior informed consent procedure on import and export (UNEP, 2013). As a result, several such pesticides have been banned or severely restricted in many countries, but few have been banned worldwide. Thus, even for substances with very high acute toxicity, different advisory bodies may reach differing conclusions with respect to hazard and risk and, consequently, legislative jurisdictions take different decisions on whether it is necessary to ban their use.

4.1.2. Food allergens

Consideration of the nature of food allergens is essential to understanding how they are evaluated and how they can be regulated. In general, food allergens are proteins, and most, if not all food proteins may be allergenic to some extent. While most foods contain proteins, over 90% of all food allergies are due to only 8 (groups of) main allergen sources (soybean, peanut, tree nuts, wheat, milk, egg, fish, crustacea) (FAIA, 2013; FDA, 2014). Food allergies have a prevalence of around 3% in the adult population. An extensive review and meta-analysis of the epidemiology of food allergy has recently been published by the European Academy of Allergy and Clinical Immunology (EAACI, 2014). The importance of this area of regulation to food safety is not only because of the large number of people potentially affected but also because of the potential serious consequences of the adverse reactions in terms of mortality and morbidity, and the impact such allergies can have on social behaviour and the quality of life.

Food allergy is an area that has traditionally tended towards a hazard—or zero-risk-based approach for safety assessment and risk management, at least for the major food allergens. In the absence of preventive treatments or therapies, the only currently feasible strategy for consumers with food allergies is to avoid the relevant allergenic foods. In the EU, legislation is in place requiring mandatory, hazard-based labelling for the presence of 14 food allergens used at any level in pre-packed foods (EC, 2003, 2006, 2011). Similarly, in the USA, 8 major foods or food group allergens have to be labelled as present (USA, 2004).

Some food labels go further than the legal requirements to label for known allergens that have been deliberately added as ingredients by including a precautionary “may contain” warning (e.g. “may contain nuts”). This is done if there is a possibility that the allergen may be present from cross-contamination during production in order to warn allergic consumers of the possible unintended presence of an allergen in a product (Spanjersberg, Knulst, Kruizinga, Van Duijn, & Houben, 2010). There is increasing recognition that “may contain” labels are being overused by manufacturers (Remington, Baumert, Marx, & Taylor, 2013). This may be a precautionary measure to protect themselves from legal claims, whereas the original intention was that they should only be used if there is a demonstrable and significant risk of cross-contamination. The proliferation of such hazard warnings is not without its downside; it can diminish the impact on the consumer of valid allergen warnings on labels and further restrict the choice of foods that allergic individuals consider it is safe to consume.

It is also recognised that a zero risk or hazard-based approach to the elimination of cross-contamination may go far beyond what is reasonable or necessary to protect human health. This is discussed further below, under risk-based approaches for food allergens.

4.1.3. Whole foods, including novel and genetically modified foods

Solely hazard-based approaches are not used for the safety assessment and regulation of whole foods, including novel or genetically modified foods; they are regulated using risk-based approaches, in which hazard identification is simply the first step. However, in the EU, in addition to safety issues, other factors, such as economics and consumer perception, can also now be taken into account in making decisions on whether to permit import or cultivation of a particular GM crop in an individual Member State.

It has long been recognized that a hazard-based approach to whole foods regulation could affect the availability of nutritionally and economically essential foods. For example, it could result in bans on traditional and commonly consumed foods that contain naturally occurring toxins (e.g. genotoxic hydrazines in mushrooms, glycoalkaloids in potatoes, cyanogenic glycosides in cassava), or on traditional food processing methods (e.g. frying or roasting of potatoes that generates the carcinogen, acrylamide), or bans on essential crops contaminated with any level of mycotoxins, which can have both potent acute toxic effects and serious chronic effects (Wu, Groopman, & Pestka, 2014). Consequently, the approach to risk management of naturally occurring toxicants and contaminants has been based on risk assessment and the setting of legal or guideline limits or tolerances that sometimes have to strike a balance between what might be considered best from the perspective of human toxicity (e.g. zero tolerance) and what is necessary to ensure that nutritional needs are met and to maintain food security, i.e. a risk-benefit approach. For example, maximum limits for chemical contaminants in the EU, including naturally occurring toxicants, often reflect levels that are ‘as low as is reasonably achievable’ (ALARA) with good manufacturing practices or good agricultural practices.

4.1.4. Pathogenic microorganisms

Microbiological risk assessment is a relatively new discipline, initiated after adoption of the World Trade Organization Agreement on Sanitary and Phytosanitary Measures in 1995 (see WTO, 2015). Hazard-based approaches, aiming at prevention or reduction of the presence of pathogenic microorganisms have traditionally been used for regulation and management. Control commonly requires a food chain approach, as end-product control is neither feasible nor effective, due to the low prevalence of contaminated products, low concentrations of microorganisms, and the potential of microorganisms to grow. Hazard-based approaches can be applied throughout the food chain from farm, through processing, packaging, retailing to purchase by the consumer, and are often effective. However, a zero risk approach is normally not feasible for microbiological agents as many hazards occur “naturally” at primary production (e.g. in the faeces of production animals and in the soil).

Microbiological criteria define the acceptability of a product, a batch of foodstuffs or a process, based on the absence, presence or number of microorganisms, and/or on the quantity of their toxins/metabolites, per unit(s) of mass, volume, area or batch (Codex Alimentarius, 1997). They can be used as tools to assess the safety and quality of foods, but cannot guarantee safety. They are traditionally defined on the basis of quantitative risk assessment and feasibility. This hazard-based approach is often useful and efficient, but it can be too stringent when the actual impact of control on the human health risk is not known.

4.1.5. Advantages and disadvantages of hazard-based approaches

There are situations in which hazard-based approaches are appropriate and these are summarised in Table 1. The advantages

Table 1
Hazard-based approaches: examples of their appropriate use, advantages and disadvantages.

Appropriate use of hazard-based approaches	Examples
Exposure conditions cannot be predicted or estimated with any confidence but there is an immediate need for rapid communication of information on potential hazards.	When there is an accident during storage or transport resulting in a major chemical release.
No threshold for the adverse effect can be identified.	Substances that are genotoxic are usually not allowed to be deliberately added to food or present as residues in food; most such substances are prevented from entering the food chain by pre-market assessments, but occasionally further testing reveals a permitted substance, or a metabolite, is genotoxic, e.g. the food colour, Red 2G.
Exposure is avoidable.	Avoidable contaminants can sometimes be eliminated completely from the food chain, e.g. avoidance of the use of extracts of *Sassafras albidum* root (which contain safrole) in food production. Use of allergenic ingredients in food can be avoided or intake by allergic consumers can be prevented through appropriate hazard-based labelling.
Use in food is not permitted in law.	Illegal adulteration, e.g. chilli powder containing non-permitted Sudan dyes.
Advantages of hazard-based approaches	**Examples**
Hazard identification is an early step in risk assessment and may offer the benefit of earlier regulatory decisions.	Substances proposed for use in food contact materials showing very low migration into food require assessment of genotoxicity in the first instance, enabling an early hazard-based decision on whether they may be used.
Do not require exposure assessments, which are a prerequisite for risk-based assessment and often have inherent uncertainties (although there are also uncertainties associated with the assessment of hazard).	Adequate exposure assessments in relevant foods may be lacking, particularly for naturally occurring, newly-discovered, or man-made environmental contaminants. Labelling requirement for allergenic ingredients used in food.
Can be particularly appropriate for the regulation and management of certain acute toxicological hazards.	Pesticides with very high acute toxicity, e.g. certain cholinesterase inhibitors.
Hazards are simpler to regulate and easier to explain to the public.	The need to eliminate avoidable substances that are both genotoxic and carcinogenic from the food chain is readily accepted by all stakeholders.
Can be perceived to be more precautionary and therefore consequent decisions are more likely to be accepted by the public than those relying on risk-based approaches.	Endocrine disruptors, e.g. some phthalate esters
Disadvantages of hazard-based approaches	**Examples**
Hazard classification and labelling of chemicals can be misunderstood and used to draw false conclusions about risk, without any consideration of potency or exposure.	Classification of substances as toxic to reproduction can have the same regulatory consequences as those for substances classified as genotoxic or carcinogenic, despite potency and exposure being important in determining reproductive risk.
Decisions are yes/no without room for accommodating any flexibility with respect to practical considerations and, as a consequence, can be overly conservative.	Recent assessments of caffeine have concluded that there is no threshold for adverse effects on fetal growth rate, yet there would be practical considerations in attempting to ban caffeine-containing products.
Hazard-based approaches for food allergens often lead to flawed assessments and actions (e.g. recalls) which are disproportionate to any risk to public health, and consequently wasteful of valuable resources.	The first half of 2015 saw numerous alerts and actions over the presence of peanut residues in cumin and almond in paprika. Risk assessments by national agencies judged the risk to public health to be acceptable, but this did not lead of itself to the end of the alerts and product withdrawals.
Hazard-based approaches for food allergens can lead to proliferation of precautionary actions by manufacturers, which go beyond the requirements of the legislation.	The proliferation of “may contain” labels for food allergens can result in direct disadvantages for allergic consumers in the form of potentially inaccurate information and limitation of choice.
Hazard-based regulation can result in the unnecessary loss of valuable products to society.	Application of the CLP regulations to pesticides can result in hazard classification, even though the risk assessment from EFSA supports continued use; products with a specific hazard pictogram or phrase may not be recommended, even though the product remains registered and safe when used as intended (with all the caveats).
Hazard-based decisions may result in less suitable substitutes being introduced, including substitutes for which less is known about their safety.	Substitution of bisphenol A in food contact materials by other, less investigated bisphenols with potentially similar activity.
Even if regulatory action is not taken as a result of hazard labelling, an agent/product is likely to be stigmatised.	In the EU, products containing any of the ‘Southampton six’ food colours must now be labelled “May have an adverse effect on activity and attention in children”; many manufacturers have now ceased using these colours.
There may be pressure to ignore future risk assessments.	Hazard-based decisions on ‘severe’ endpoints such as carcinogenicity and teratogenicity may lead to a precautionary approach, whereby even sound risk assessments are subsequently ignored; an example where this could have occurred is the teratogenicity of sulfoxaflor, which has now been shown not to be relevant to humans.
Hazard-based decisions can divert economic and scientific resources into further investigation of agents/products for which risk assessments show there is reasonable certainty of no harm during normal handling and use.	Considerable resources have been expended into research on non-genotoxic rodent carcinogens, a number which produce tumours by a mode of action that is not relevant to humans, for example the hepatocarcinogenicity of the insect repellent metofluthrin.
Inappropriate application of hazard-based decisions can undermine confidence in innovation.	An example of this can be found in current attitudes towards genetically modified organisms and the decreasing research base in Europe.
Risk management action may not be taken under a hazard-based approach if perceived excessive in the context of the benefits of the food, whereas if a risk-based approach is used, proportionate management action can be taken.	Methylmercury in fish.

and disadvantages of hazard-based approaches are also summarised in Table 1, with examples given.

4.2. Risk-based approaches

Risk-based approaches generally follow the well-known risk assessment paradigm, comprising four steps — hazard identification, hazard characterisation, exposure assessment and risk characterisation (WHO, 2009). It is recognised that risk-based approaches to food safety will always carry a certain degree of uncertainty, both in relation to the toxicological data and the exposure estimates. A scientific approach to the estimation of uncertainties enables them to be characterised and, where possible, quantified.

At the risk characterisation stage, there is a long-established history of taking account of uncertainties in toxicological data and in the extrapolation from laboratory animal studies to humans. This can be done by the application of default or chemical-specific uncertainty factors to NOAELs or benchmark doses in order to derive health-based guidance values or interpret margins of exposure (EFSA, 2009; WHO, 2009). Default uncertainty factors are usually 100-fold, but they can be lower or higher, depending on the available data. The toxicological science community is also now devoting considerable effort to improving the prediction of adverse effects on human health, for example with the use of *in vivo* biomarkers, or the use of largely *in vitro* human-derived test systems, coupled with identification of human biochemical pathways that may be perturbed by chemicals (e.g. the US Environmental Protection Agency's Tox21 program (Tice, Austin, Kavlock, & Bucher, 2013)).

Good exposure estimates and knowledge of their uncertainties are prerequisites for reliable risk characterisation (Kettler et al., 2015). Methods, including probabilistic methods, are available for defining uncertainties in dietary exposure estimates (EFSA, 2006; WHO, 2008), but to improve risk-based approaches, better methods are needed for quantitation of uncertainties in exposure assessments, which are inherent in food consumption, food categorisation, and occurrence data. Currently, estimates and predictions of human exposure to substances in food can involve the use of conservative default assumptions. The conservative nature of the default assumptions can be seen from the increasing evidence that direct measurements (biomonitoring) in humans usually demonstrate much lower exposures than those derived from exposure estimates, as has been shown for example, for phthalates and bisphenol A (Qian, Chen, Kransler, & Zaleski, 2014; EFSA, 2015). While conservative default assumptions build in a high degree of safety in any risk-based approach, they may also result in unnecessary actions when overestimated exposures exceed health-based guidance values. Thus, as well as better methods for exposure estimation from occurrence and consumption data, there is a need for continuing development and greater use of human biomarkers of exposure. This will enable better verification of exposure estimates and measurement of aggregate exposure from all routes.

Risk communication strategies are also needed to convey the complexities of different levels of uncertainty in the risk assessment process. This will ensure that there is increasing awareness among regulators, manufacturers, and the general public of the consequences of uncertainty for risk-based conclusions on food safety, which can never be absolute.

4.2.1. Chemicals

Risk-based approaches are used worldwide for the assessment of avoidable and unavoidable contaminants in food, whether intentionally added or non-intentionally present, and whether natural or man-made. For toxicological endpoints considered to have a threshold, the data are used to derive health-based guidance values or margins of exposure. These may then be 'translated' into legislation as maximum levels (MLs), action levels or tolerances in foodstuffs, designed to ensure that consumer exposures, including high percentile consumer exposures, are of low risk. For contaminants exhibiting toxicity that is considered to be without a threshold, for example genotoxins/genotoxic carcinogens, risk-based approaches allow the estimation of margins of exposure judgement on whether exposures are of no, low or high concern (Barlow et al., 2006).

Risk-based approaches are also used worldwide for assessment of food additives, flavourings and substances used in food contact materials, with the exception that genotoxic substances are not generally permitted in food, which is a hazard-based decision.

Risk-based approaches are also widely used for evaluation of chemical residues present in food from the use of plant protection products and veterinary products. In the EU, residues from plant protection products are evaluated by EFSA and the EU Member States and those from veterinary products are evaluated by the European Medicines Agency (EMA). Consumer safety for both is assured by risk assessment, whereby the legally permitted residues present in food following use according to good (agricultural or veterinary) practice would not give rise to consumer exposures greater than the respective health-based guidance values. In such risk assessments, due consideration is given to mode of action and margin of exposure so that it may be possible to conclude that the risk even of an effect such as carcinogenicity is negligible at any conceivable dietary exposure. For example, the renal carcinogenicity of the fungicide chlorothalonil is secondary to the target organ toxicity of the compound via a well-established mode of action, involving the formation of thiol metabolites (Wilkinson & Killeen, 1996). Protection against the risk of renal toxicity will ensure that there is negligible risk of carcinogenicity. However, independent of such risk assessment, the substances are assessed for certain hazards, including carcinogenicity and reproductive toxicity, by a different organization, ECHA. Whilst often using the same toxicological database, a regulatory consequence, based solely on hazard assessment is independent of scenario. This could mean that, for example, whilst the carcinogenic risk to humans from residues of a pesticide in food is considered negligible, the pesticide could receive a hazard classification for carcinogenicity, thereby markedly restricting its use. Clearly harmonisation in interpretation of the toxicological database for such chemicals by the respective assessors would be highly desirable.

4.2.2. Food allergens

For food allergens, there is a need for discussion and guidance on what levels of the major allergens should trigger a precautionary warning and thus on whether and what level of residual risk may be acceptable. This requires a quantitative, risk-based approach. For example, in the EU regulations, in addition to the mandatory, hazard-based labelling of the presence of certain allergens in foods discussed earlier, there are provisions for exemption from mandatory labelling for ingredients derived from these allergens, based on a qualitative, risk assessment approach (EC, 2000b). Progress in this area would enable a framework for food allergen risk assessment to be developed that could, for example, be applied to exemptions from labelling of ingredients derived from allergens and to deciding on precautionary warning for allergens unintentionally present in food ('may contain' labels).

To facilitate moves towards a quantitative, risk-based approach for food allergen regulation in the EU, EFSA was asked to give an opinion on the evaluation of allergenic foods and food ingredients for labelling purposes (EFSA, 2013). EFSA considered the methods available for the quantification of food allergens and the question of

whether thresholds could be derived, below which the majority of sensitised consumers would not be at risk of developing severe allergic reactions. EFSA noted that, although the derivation of individual and population thresholds is a matter of scientific judgement, the setting of reference doses and action levels would, in addition, require risk management decisions which were outside EFSA's remit (EFSA, 2013). Thus at present there is no agreement on threshold levels in the EU.

Elsewhere, many efforts have been made during the last decade to develop databases and approaches for quantitative risk assessment of food allergens that could support risk-based management decision making. These are now being used in the development of guidance for precautionary allergen labeling or for assessing the risk of products with (possible) unintended allergen presence that may be on the market. A very illustrative case study was published on the dilemmas of hazard-based and qualitative risk assessment-based approaches, in which it was shown that these approaches easily lead to inconclusive information or unpractical conclusions (Spanjersberg, Kruizinga, Rennen, & Houben, 2007). In the same publication, a proof of principle for probabilistic quantitative risk assessment for food allergy was given as an alternative. This approach was further developed and applied to other cases (see for instance Kruizinga et al., 2008 and Spanjersberg et al., 2010) and now is generally considered the best approach for allergen risk assessment for risk management purposes (Madsen et al., 2009).

Probabilistic risk characterisation methods can also be used to calculate reference doses that would comply with defined levels of (accepted) risks. A guidance system suitable for deciding on the use of precautionary labelling has been developed by the Allergen Bureau in Australia and New Zealand: the Voluntary Incidental Trace Allergen Labeling (VITAL 2.0). Reference doses were calculated from population distribution modelling of minimal eliciting doses for allergic reactions. A residual risk of 1% mild objective reactions was agreed upon by stakeholders and taken as a starting point for the elaboration of these reference doses (Allen et al., 2014; Taylor et al., 2014).

Several other papers have addressed the development and use of quantitative approaches in risk assessment and safety standard development for food allergy and have addressed the advantages of these approaches (see among others Madsen et al., 2014; Crevel et al., 2014a, b, c). Further development of threshold data bases and consensus on the application of such knowledge will bring this area of risk assessment to a higher level. Critical analyses and discussions on data gaps and uncertainty will be needed to direct future research and to reach consensus and acceptance of these approaches (see for instance Klein Entink et al., 2014; Taylor et al., 2015).

4.2.3. *Whole foods, including novel and genetically modified foods*

The safety of novel and genetically modified (GM) foods or ingredients is assessed using risk-based approaches that evaluate any potential nutritional, microbiological, toxicological or allergenic hazards. This involves establishing whether the novel or GM food/ingredient is substantially equivalent to a traditional food or food component. If there is a traditional counterpart, a comparative assessment of the novel or GM food/ingredient and the traditional counterpart is undertaken and the differences are probed to identify and characterise any new hazards or changed levels of exposure to known, existing toxicants. This approach recognises that traditional foods may be hazardous but that typical custom and practice in preparation and intake (exposure) will be safe for the majority of the population. At the same time it does not overlook the potential for toxic effects or allergic responses, including life threatening anaphylaxis in individuals. This comparative assessment can include using *in silico*, *in vitro*, *in vivo* and human studies if available/necessary. If there is no traditional counterpart, then the novel or GM food/ingredient must be evaluated for any potential hazards on a case-by-case basis, as for chemicals. This may include toxicological testing of the whole food/ingredient, or testing of a novel chemical found to be present in the food/ingredient, or testing of a chemical naturally found in the traditional counterpart but present in the novel or GM food at a much higher concentration. The toxicological testing is mostly in laboratory animal species and aimed at establishing "no-observed-adverse-effect-levels" (NOAELs). Exposure assessment is then undertaken, using information on the anticipated use of the novel or GM food/ingredient, anticipated intake including any geographical differences, whether it will replace other foods, whether any of the replaced foods are significant nutritional sources, and whether there may be any special 'at risk' population groups. Exposure is then compared with NOAELs. If concentrations of known, existing toxicants in a novel or GM food/ingredient are increased, exposure estimates can be compared with tolerable daily intakes, if these have been previously established.

4.2.4. *Pathogenic microorganisms*

Consideration of the nature of microbiological agents illustrates why development of risk-based approaches, in addition to established hazard-based approaches, is necessary. Low concentrations may have the potential to cause illness and low concentrations in the food chain can result in high exposure due to the growth potential of microorganisms. Detection of low concentrations and the proper identification of pathogens offer practical methodological challenges. Quantification of microorganisms is complex as the measured units (e.g. a colony forming unit (CFU), the countable entity growing on a plate) are not necessarily individual bacteria. For microorganisms, the species concept is debated. Bacteria can occur in different cellular states, they can change their characteristics during their life through adaptation to the environment, and new strains can emerge due to mutation and selection. At the level of hazard characterisation, information from humans is normally only available on acute illness and it is difficult to define dose–response relationships. The probability of illness is a function of dose, but it is difficult to establish the probability of illness after a single exposure. There are few human data to support the development of dose–response relationships as they only come from "volunteer" experiments and from outbreaks of (acute) illness. In general, animal models cannot be adequately used for hazard characterisation of pathogenic microorganisms.

The benefit of developing risk-based approaches can be illustrated by the problem of *Campylobacter* in poultry meat. *Campylobacter* is the most frequently reported bacterial, foodborne zoonosis in the EU, with 200,000 human cases reported and about 9 million cases estimated per year (EFSA, 2014). The illnesses caused range from diarrhoea, reactive arthritis, Guillain-Barre syndrome, inflammatory bowel disease, through to death. Poultry are generally considered the main source of the pathogen and *Campylobacter* can naturally occur in chicken faeces. As the prevalence of this pathogen in poultry is often high, hazard-based control is not realistic because banning the supply and sale of fresh chicken is not a societally acceptable option. Biosecurity is difficult and expensive, and common production methods for fresh broiler meat production do not eliminate the pathogen. Chemical decontamination of carcasses is not allowed in the EU, though it is allowed in some countries elsewhere in the world. Common food preparation methods do not completely eliminate it either; cooking does kill the bacteria, but maintaining good hygiene is difficult (Havelaar et al., 2007; EFSA, 2011).

Instead, a risk-based approach has been proposed for food safety

control by setting so called "risk based" microbiological criteria (EFSA, 2011; Nauta, Sanaa, & Havelaar, 2012, 2015). Here, a predefined number of samples are taken from batches of poultry meat. The criterion is defined by an acceptable number of samples with, for example, not more than 1000 cfu/g, or by an acceptable risk estimate on the basis of the samples. It can be shown that compliance to such a criterion can reduce the public health risk considerably. Risk managers can decide on the preferred criterion after balancing the residual risk against the economic consequences and practical feasibility.

4.2.5. Advantages and disadvantages of risk-based approaches

The advantages and disadvantages of risk-based approaches are summarised in Table 2, together with examples.

5. Discussion and conclusions

Legislation in the EU and elsewhere in the world currently includes a mix of both hazard-based and risk-based approaches for ensuring food safety. One of the questions considered at the workshop was whether there is better consumer protection from the use of risk-based approaches, from the use of hazard-based approaches, or from the appropriate use of both. It was concluded that both types of approach have their place, depending on the context. While hazard-based approaches are used in some contexts (e.g. for acute and potent hazards, avoidable contaminants, genotoxic substances, allergenic ingredients, etc), risk-based approaches are most widely used around the world for chemical substances in food, and the value of risk-based approaches in areas hitherto managed mostly by hazard-based approaches (e.g. food allergens, microbiological risks) is being increasingly recognised.

When regulation of a particular type of agent in food is managed using a wholly hazard-based approach or a wholly risk-based approach, there may be questions about whether that is optimal, but in general conflicts do not arise. A problem can arise when both types of approach are used in regulation by separate agencies, which address different aspects of the same agent/substance that is present in food. Currently in Europe, pesticides and biocides are subject to both hazard-based CLP regulation of the chemical *per se*, overseen by ECHA, and risk-based regulation regarding residues in food, overseen by EFSA. Such separation of toxicological decision-making can result in hazard-based restrictions on marketing and use, such that products containing the chemical can no longer be used, whereas risk-based assessments for those exposed, either as operators or as consumers, show that there is reasonable certainty that no harm will result. Hazard-based regulatory decisions that do not take account of risk assessments can also trigger problematic issues concerning replacements for certain chemicals, if alternatives are used on which there is much less knowledge. Consideration needs to be given to how to avoid the consequences of the separation of hazard- and risk-based assessment, which can lead to contradictory, confusing and ultimately unnecessary actions.

Another problem with both hazard-based approaches in the food area is that it is not possible to undertake any comparison with benefit. Benefit encompasses not only the area of nutritional benefit, which can be weighed against known or potential toxicological risks in risk-benefit analyses of individual foods (BRAFO, 2012), but also encompasses food security, which includes physical availability of food, economic and physical access to food, utilization of food, and stability of the food supply (FAO, 2008). Hitherto, benefit considerations have often been narrowly focused on nutritional aspects or have not been considered at all. This has the potential to lead to bias in the overall conclusions of regulators and risk managers, who may not have been presented with the benefits of particular foods.

The aim of food legislation should be to ensure the achievement of the right balance between minimising potential risks to human health and the environment and maximising the benefits to society.

6. Way forward and the challenges to be met

The increasing use of risk-based approaches across the entire food sector requires agreement among stakeholders on how to deal with risks. This would include a common understanding that appropriate risk management for foods may depend on the context of both risks and benefits. In order to reach a common understanding on the value of risk-based methods and risk-benefit methods for ensuring food safety and security, there is a need for regular and meaningful dialogue between risk assessors, legislators and risk managers, risk communicators, food producers, food retailers, and the general public as consumers. Among risk assessors, including those from different advisory and regulatory bodies, there is a need for agreed procedures on optimal approaches to data evaluation.

These challenges will entail not only a good understanding of risk assessment and an appreciation of the differences between hazard- and risk-based approaches, but also due recognition of differences in risk perception and risk acceptance among stakeholders and a willingness by all stakeholders to consider another perspective.

Another challenge is the identification of risks for chemicals on which there are currently very few data. This is a resource issue, both for society, because of the cost of testing and limited testing facilities, and for the prioritisation of tasks for risk assessment bodies.

A further challenge is to increase understanding of the uncertainties in risk assessment. This encompasses how they can vary in type and in their impact on a risk assessment, and how uncertainties should be interpreted. Above all, there is a need to ensure transparency about the uncertainties in risk assessments and that these are explained to all stakeholders.

The sharing of advances in risk-based methodologies will facilitate harmonisation and consistency across food sectors, across regions and across other chemical sectors. Further advances in the science of exposure assessment will benefit all sectors. Risk assessments need to be transparent, of high quality and address uncertainties. Better clarity, consistency and communication of findings by risk assessors and risk communicators and the use of opportunities, such as stakeholder forums and the teaching of risk assessment in school and university curricula, will facilitate wider understanding of the issues and improve public trust in the outcomes of risk assessment.

For all stakeholders, there is a need to understand risks in context as this can influence views on the levels of risk that are considered to be acceptable. For example, the risks of one substance or product that may no longer be permitted/available need to be compared with those of potential replacements, or with other chemicals used in the same sector, or with natural chemicals that can produce the same effect of concern. Food risks also need to be seen alongside benefits in order to make a balanced decision.

Scientific aspects are an important component of a common language for all the stakeholders. Adoption of science-based risk assessment approaches provides a way of applying common principles and approaches consistently for all stakeholders, based on objective evidence and its inherent uncertainties. Communication and the use of appropriate language is one of the challenges.

These are immense challenges, not least because they require concerted efforts across multiple disciplines and professions, in

Table 2
Risk-based approaches: examples of their advantages and disadvantages.

Advantages of risk-based approaches	Examples
When there are sufficient data, risk-based approaches provide practical information concerning the likely or probable risk to the exposed population, rather than a hypothetical indicator of harm which may never be realised.	Risk assessments of unavoidable contaminants that are genotoxic and carcinogenic, using the margin of exposure approach, can indicate which (sub) populations and what foods/food products should be targeted for risk reduction measures, e.g. acrylamide.
For chemical substances, the risk to human health depends on the toxicological potency of the substance, and the frequency and duration of exposure; only risk-based approaches offer information on these aspects.	Numerous published risk assessments such as those on non-genotoxic carcinogens that act secondarily to perturbations of biochemistry of physiology, e.g. agents causing C-cell follicular tumours of the thyroid, agents causing tumours of the liver by activation of the PPARα receptor.
Quantitative approaches can give insight into the magnitude of risks and can be used as a basis for deriving "safe" levels of exposure.	Derivation of health-based guidance values (ADI, TDI, etc) for substances that are deliberately added, or present as residues or as contaminants in food.
Can inform on the level of risk reduction that can be achieved, guiding risk management decisions and consumer choice.	Consumer advisories on methylmercury in fish. Impact on consumer risk of changing maximum levels for aflatoxins in nuts.
Uncertainties can be estimated, at least qualitatively, and provide guidance to manage risks.	In the risk assessment of brominated flame retardants, although there were data gaps, it was possible to provide guidance to risk managers as to which ones should be prioritised for action.
Can have substantial socio-economic benefits over hazard-based approaches.	Elimination of microbiological hazards in foods is usually not feasible, as it is too costly and not accepted by consumers.
Risk-benefit assessment is possible, which allows the optimisation of health and socio-economic benefits.	Fortification of food with folic acid. Fish containing nutritionally beneficial protein and oils but also undesirable contaminants such as methylmercury and polychlorinated biphenyls. Soy containing nutritionally beneficial protein, vitamins and minerals but also isoflavones with potential benefits and risks due to their oestrogenic activity.
Comparison of risks and quantification of risks from different uses, and for prioritisation purposes, is possible.	Risk-based approaches enabled the identification of the major sources of exposure (and risk) to anti-thyroid substances. In the risk assessment of aspartame, it was possible to establish that other sources of methanol in the diet were of greater potential concern. EFSA's risk ranking activities.
Can benefit public health by avoiding wastage of foods that are not harmful and the unnecessary costs of reducing hazards where there would be little or no consumer benefit, whilst protecting consumers by ensuring high standards of food safety.	Decisions on whether a food should be recalled or withdrawn when a new hazard is discovered. Use of risk-based microbiological criteria for poultry.
Can help avoid unnecessary stigmatisation of substances for which there are no known safer alternatives.	In the case of certain crop protection chemicals where a derogation may be given to use a particular fall-back substance in the case of urgent agricultural need.
Can provide opportunities to facilitate stakeholder discussions on the important considerations of a risk assessment.	In incident situations, e.g. food adulteration, or occurrence of an additive or contaminant above a legally permitted level. The approval of a novel ingredient.
Risk-based assessments of chemical residues enable the effective use of agricultural and veterinary products (pesticides, veterinary drugs) whilst ensuring a high level of public health protection.	Supporting decisions on what crops a pesticide can be permitted for use and on whether maximum residue levels (MRLs) on crops are compatible with the risk assessment
For microbial pathogens risk based approaches can inform on the impact of expensive product testing sampling programs, and improve their efficiency.	Risk assessment allows the evaluation of the impact of the establishment of microbiological criteria in terms of potential risk reduction and costs of rejection of contaminated food lots.
Risk based approaches for microorganisms allow a quantification of risk and risk prioritization.	Quantitative risk characterization allows evaluation of risk mitigation strategies in cost effectiveness studies, and comparison of hazards for risk prioritization.
Disadvantages of risk-based approaches	**Examples**
Take longer to perform than hazard-based approaches.	Risk assessments of many commonly occurring contaminants can be very time consuming and show duplication of effort around the world, e.g. cadmium, dioxins.
Require more data.	Many newly-discovered contaminants in food have few toxicity or exposure data.
Chemical occurrence and relevant food consumption data are not always available for all food categories or all countries.	Adequate exposure assessments in relevant foods may be lacking, particularly for naturally occurring, newly-discovered, or man-made environmental contaminants.
Considerable expertise is required for exposure modelling and risk assessment.	This is particularly true of higher tier assessments, which may involve probabilistic approaches to exposure and physiologically-based pharmacokinetic modelling for toxicity.
Require the wider development of technical capacity for risk assessment (e.g. in regulatory agencies, industry).	Many governments are dependent on risk assessments made by other bodies, e.g. JECFA; smaller food industries do not have in-house capacity.
Can include considerable uncertainty in making extrapolations from animal data to derive points of departure for risk assessment.	When comprehensive toxicity data are lacking, this often results in the use of very large uncertainty factors. In all exposure assessments of microorganisms, due to insufficient data and the potential for growth and inactivation between point of measurement and the actual exposure.
Can include considerable uncertainty in exposure estimates.	When data are lacking, default "worst-case" estimates may have to be used, e.g. it is assumed that a deliberately added substance will be present in all relevant foods at the highest permitted level. When exposure is estimated from dietary surveys, there is an inherent uncertainty in assessing food consumption. When exposure is estimated by different methodologies, different periods of time, different age groups, etc.

(*continued on next page*)

Table 2 (*continued*)

Advantages of risk-based approaches	Examples
A common understanding and agreement on uncertainty factors is needed.	EFSA has recently published draft guidance on the assessment and expression of uncertainty in risk assessments but it has yet to be finalised and the extent to which it will be adopted outside of EFSA is not clear at present. ILSI is working on assessing uncertainty in exposure estimates (see Kettler et al., 2015) to emphasise the inherent uncertainty in some steps of risk assessment and to provide directions for the quantification of uncertainty, although uncertainty cannot be fully eliminated.
Require agreement among stakeholders on how to deal with risks (risk perception and risk acceptance), although even hazard-based approaches may require such considerations when exposure can occur below the limit of detection.	How to deal with endocrine active substances. GM crops and traits arising from so-called new breeding technologies.
Use and acceptance of risk-based approaches requires better understanding of the underlying science by all relevant stakeholders, including consumers.	The public is overwhelmed by contradictory messages on the hazard or risk for a variety of food-related issues and, understandably, there is difficulty in knowing whom to trust; this complicates efforts to communicate effectively the distinction between hazard and risk, and the implications.

which there are no clear leads among professional organisations, consumer bodies, academia, government and international bodies for education and communication about risk assessment in general.

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References

Allen, K. A., Remington, B. C., Baumert, J. L., Crevel, R. R. W., Houben, G. F., Brooke-Taylor, S. … Taylor, S. L. (2014). Allergen reference doses for precautionary labeling (VITAL 2.0): clinical implications. *Journal of Allergy and Clinical Immunology, 133*, 156–164.

Barlow, S., Renwick, A. G., Kleiner, J., Bridges, J. W., Busk, L., Dybing, E. … Würtzen, G. (2006). Risk assessment of substances that are both genotoxic and carcinogenic: report of an International conference organized by EFSA and WHO with support of ILSI Europe. *Food and Chemical Toxicology, 44*, 1636–1650.

BRAFO. (2012). Benefit and risk analysis for foods (BRAFO): qualitative and quantitative comparison of human health risks and benefits of food and food components. In A. Boobis, J. Hoekstra, B. Watzl, H. Verhagen, K. Schütte, & S. Vidry (Eds.), *Food and chemical toxicology, 50* pp. S683–S736).

Callan, S. J., & Thomas, J. M. (2013). *Environmental economics and management: Theory, policy and application* (6th ed.). Mason, OH, USA: South-Western Cengage Learning.

Chakraborty, S. (2012). *The risk versus hazard debate: Reconciling inconsistencies in health and safety regulation within the UK and across the EU. The foundation for law, Justice and society in affiliation with the centre for socio-legal studies*. UK: University of Oxford. Available at: http://www.fljs.org/sites/www.fljs.org/files/publications/Chakraborty.pdf.

Codex Alimentarius. (1997). *Recommended international code of practice – general principles of food hygiene*. CAC/GL 21-1997. Rome: Codex Alimentarius Joint Office. Available at: http://www.codexalimentarius.org/standards/list-of-standards/.

Codex Alimentarius. (1999). *Principles and guidelines for the conduct of microbiological risk assessment*. CAC/GL-30(1999). Food and Agriculture Organisation Corporate Document Repository. Available at: http://www.fao.org/docrep/005/y1579e/y1579e05.htm.

Codex Alimentarius. (2011). *Guidelines for the control of campylobacter and salmonella in chicken meat*. CAC/GL 78-2011. Available at: http://www.codexalimentarius.org/input/download/standards/11780/CXG_078e.pdf.

Crevel, R., Barbara, B.-W., Taylor, S. L., Houben, G., & Mills, C. (2014c). Thresholds or "how much is too much". Chapter 5. In C. B. Madsen, R. W. R. Crevel, & C. Mills (Eds.), *Risk management for food allergy* (pp. 77–99). Taylor: S.L. Elsevier Inc. ISBN 978-0-12-381988-8.

Crevel, R. W., Baumert, J. L., Baka, A., Houben, G. F., Knulst, A. C., Kruizinga, A. G. … Madsen, C. B. (2014a). Part II: development and evolution of risk assessment for food allergens. *Food and Chemical Toxicology, 67*, 262–276.

Crevel, R. W., Baumert, J. L., Luccioli, S., Baka, A., Hattersley, S., Hourihane, J. O. … Chung, Y. J. (2014b). Part III: translating reference doses into allergen management practice: challenges for stakeholders. *Food and Chemical Toxicology, 67*, 262–276.

EAACI. (2014). In A. Murao, & G. Roberts (Eds.), *EAACI food allergy and anaphylaxis guidelines*. Zurich, Switzerland: European Academy of Allergy and Clinical Immunology. Available at: http://www.eaaci.org/attachments/Food%20Allergy%20Supplementary%20V1.pdf.

EC. (1967). Directive 67/548/EEC. Classification, packaging and labelling of dangerous substances of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances. *Official Journal of the European Communities, 196*, 234–256, 16.8.67. Available at: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:31967L0548&from=EN.

EC. (1999). Directive 1999/45/EC of the European parliament and of the council of 31 May 1999 concerning the approximation of the laws, regulations and administrative provisions of the member states relating to the classification, packaging and labelling of dangerous preparations. *Official Journal of the European Communities*. L 200/234–256, 30.7.1999. Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1999L0045:20090120:EN:PDF.

EC. (2000a). *Communication from the commission on the precautionary principle*. Brussels 02.02.2000. COM(2000) 1. Available at: http://ec.europa.eu/dgs/health_consumer/library/pub/pub07_en.pdf.

EC. (2000b). Directive 2000/13/EC of the European parliament and of the Council of 20 March 2000 on the approximation of the laws of the member states relating to the labelling, presentation and advertising of foodstuffs. *Official Journal of the European Communities*. L 109/29-42, 6.5.2000. Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2000:109:0029:0042:EN:PDF.

EC. (2002). REGULATION (EC) no 178/2002 of the european parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. *Official Journal of the European Communities*. L.31/1–24, 1.2.2002. Available at: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32002R0178&from=en.

EC. (2003). Directive 2003/89/EC of the European Parliament and of the Council of 10 November 2003 amending directive 2000/13/EC as regards indication of the ingredients present in foodstuffs. *Official Journal of the European Union*. L 308/15-18, 25.11.2003. Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:308:0015:0018:EN:PDF.

EC. (2006). Commission directive 2006/142/EC of 22 December 2006 amending Annex IIIa of directive 2000/13/EC of the European Parliament and of the Council listing the ingredients which must under all circumstances appear on the labelling of foodstuffs. *Official Journal of the European Union*. L 368/110-111, 23.12.2006. Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:368:0110:0111:EN:PDF.

EC. (2008). Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. *Official Journal of the European Union*. L 353/1-1355, 31.12.2008. Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:353:0001:1355:EN:PDF.

EC. (2009a). *Special Eurobarometer. Europeans' attitudes toward chemicals in consumer products: Risk perception of potential health hazards*. Brussels: European

Commission. Available at: http://ec.europa.eu/public_opinion/archives/ebs/ebs_314_en.pdf.
EC. (2009b). Regulation (EC) No 1107/2009 of the European parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing council directives 79/117/EEC and 91/414/EEC. *Official Journal of the European Union*. L 309/1-50, 24.11.2009. Available at: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32009R1107&from=EN.
EC. (2010). *Special Eurobarometer 354. Food-Related risks*. Conducted by TNS Opinion and Social, Brussels, Belgium, at the request of the European Food Safety Authority. Brussels: European Commission. Available at: http://ec.europa.eu/public_opinion/archives/ebs/ebs_354_en.pdf.
EC. (2011). Regulation (EU) No 1169/2011 of the European parliament and of the Council of 25 October 2011 on the provision of food information to consumers, amending regulations (EC) No 1924/2006 and (EC) No 1925/2006 of the European parliament and of the Council, and repealing commission directive 87/250/EEC, council directive 90/496/EEC, commission directive 1999/10/EC, Directive 2000/13/EC of the European parliament and of the Council, commission directives 2002/67/EC and 2008/5/EC and commission Regulation (EC) No 608/2004. *Official Journal of the European Union*. L 304/18-63, 22.11.2011. Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ%3AL%3A2011%3A304%3A0018%3A0063%3AEN%3APDF.
EC. (2012). Regulation (EU) No 528/2012 of the European parliament and of the Council of 22 May 2012 concerning the making available on the market and use of biocidal products. *Official Journal of the European Union*. L 167/1-123, 27.6.2012. Available at: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32012R0528&from=EN.
ECHA. (2009). *Introductory guidance on the CLP regulation*. Finland: European Chemicals Agency. ECHA-09-G-01-EN, 25.08.2009. Available at: http://echa.europa.eu/documents/10162/13562/clp_introductory_en.pdf.
ECHA. (2014). *Guidance on information requirements and chemical safety assessment. Chapter R.11: PBT/vPvB assessment. Version 2.0*. November 2014. Available at: http://echa.europa.eu/documents/10162/13632/information_requirements_r11_en.pdf.
EFSA. (2006). Guidance of the scientific committee on a request from EFSA related to Uncertainties in Dietary Exposure Assessment. *The EFSA Journal, 438*, 1–54. Available at: http://www.efsa.europa.eu/en/efsajournal/pub/438.htm.
EFSA. (2009). Guidance of the scientific committee on a request from EFSA on the use of the benchmark dose approach in risk assessment. *The EFSA Journal, 1150*, 1–72. Available at: http://www.efsa.europa.eu/en/efsajournal/doc/1150.pdf.
EFSA. (2011). Scientific opinion on Campylobacter in broiler meat production: control options and performance objectives and/or targets at different stages of the food chain. *EFSA Journal, 9*(4), 2105. Available at: http://www.efsa.europa.eu/en/efsajournal/pub/2105.htm.
EFSA. (2013). Scientific opinion on the evaluation of allergenic foods and food ingredients for labelling purposes. EFSA panel on dietetic products, nutrition and allergies (NDA). *EFSA Journal 2014, 12*(11), 3894. Available at: http://www.efsa.europa.eu/en/efsajournal/doc/3894.pdf.
EFSA. (2014). *Campylobacter factsheet*. Available at: http://www.efsa.europa.eu/en/corporate/doc/factsheetcampylobacter.pdf.
EFSA. (2015). Scientific opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs: Part I – exposure assessment. *EFSA Journal 2015, 13*(1), 3978. Available at: http://www.efsa.europa.eu/en/efsajournal/pub/3978.htm.
FAIA. (2013). *Allergy and intolerance*. London, UK: Food Additives and Ingredients Association. Available at: http://www.faia.org.uk/food-sensitivity/.
FAO. (2008). *An introduction to basic concepts of food security*. Food and Agriculture Organisation. Available at: http://www.fao.org/docrep/013/al936e/al936e00.pdf.
FAO. (2013). *Highly hazardous pesticides should be phased out in developing countries*. Food and Agriculture Organisation. Available at: http://www.fao.org/news/story/en/item/180968/icode/.
FDA. (2014). *United States public law C. Food allergen labelling and consumer protection act of 2004 (Public law 108-282, title II)* (pp. 905–911). Available at: http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/Allergens/ucm106187.htm.
Hammitt, J. K., Wiener, J. B., Swedlow, B., Kall, D., & Zhou, Z. (2005). Precautionary regulation in Europe and the United States: a quantitative comparison. *Risk Analysis, 25*, 1215–1228.
Hansen, J., Holm, L., Frewer, L., Robinson, P., & Sandøe, P. (2003). Beyond the knowledge deficit: recent research into lay and expert attitudes to food risks. *Appetite, 41*, 111–121.
Hattersley, S., Ward, R., Baka, A., & Crevel, R. W. (2014). Part I: advances in the risk management of unintended presence of allergenic foods in manufactured food products – an overview. *Food and Chemical Toxicology, 67*, 255–261.
Havelaar, A. H., Mangen, M.-J., de Koeijer, A. A., Bogaardt, M.-J., Evers, E. G., Jacobs-Reitsma, W. F. … Nauta, M. J. (2007). Effectiveness and efficiency of controlling Campylobacter on broiler chicken meat. *Risk Analysis, 27*, 831–844.
Idrovo, A. J. (2014). Food poisoned with pesticide in Bihar, India: new disaster, same story. *Occupational and Environmental Medicine, 71*, 228.
IFCS. (2003). *Acutely toxic pesticides initial input on extent of problem and guidance for risk management*. International Forum on Chemical Safety. IFCS/FORUM-IV/10w. Original: English 23 April 2003. Available at: http://www.who.int/ifcs/documents/forums/forum4/en/10w_f4_en.pdf?ua=1.
IPCS. (2004). *IPCS risk assessment terminology*. Harmonization Project Document No. 1. Geneva: World Health Organisation. Available at: http://www.who.int/ipcs/methods/harmonization/areas/ipcsterminologyparts1and2.pdf?ua=1.
IPCS. (2009). Glossary of terms, annex 1. In , *Environmental health criteria: 240. Principles and methods for the risk assessment of chemical in food*. Geneva: World Health Organisation. Available at: http://www.who.int/foodsafety/publications/chemical-food/en/.
Kettler, S., Kennedy, M., McNamara, C., Oberdörfer, R., O'Mahony, C., Schnabel, J. … Tennant, D. (2015). Assessing and reporting uncertainties in dietary exposure analysis: mapping of uncertainties in a tiered approach. *Food and Chemical Toxicology, 82*, 79–95.
Kishi, M. (2002). IFCS: acutely toxic pesticides. In *International forum on chemical safety*. Available at: http://www.who.int/heli/risks/toxics/bibliographyikishi.pdf.
Klein Entink, R. H., Remington, B. C., Blom, W. M., Rubingh, C., Kruizinga, A., Baumert, J. L. … Houben, G. F. (2014). Food allergy population thresholds: an evaluation of the number of oral food challenges and dosing schemes on the accuracy of threshold dose distribution modeling. *Food and Chemical Toxicology, 70*, 134–143.
Kruizinga, A. G., Briggs, D., Crevel, R., Knulst, A., van de Bosch, L., & Houben, G. (2008). Probabilistic risk assessment model for allergens in food: sensitivity analysis of the minimum eliciting dose and food consumption. *Food and Chemical Toxicology, 46*, 1437–1443.
Laidi, Z. (2010). Is Europe a risk averse actor? *European Foreign Affairs Review, 15*, 411–426.
Ley, P. (1995). *Effectiveness of label statements for drugs and poisons*. GPO Box 84, Canberra ACT 2601: University of Sydney, Australian Health Ministers' Advisory Council, Australian Government Publishing Service. , as quoted in the Inter-Organization Programme for the Sound Management of Chemicals Draft Report on the responses to the call on chemical hazard communication, December 1996, ISBN 0644 45335 4.
Lofstedt, R. (2011). *Risk versus Hazard; EU requires a fundamental rethink of risk policy*. IHS Chemical Week, September 26, 2011. Available at: http://www.chemweek.com/chem_ideas/Guest-Author/Risk-Versus-Hazard-EU-Requires-a-Fundamental-Rethink-of-Risk-Policy_37786.html.
Madsen, C., Hattersley, S., Buck, J., Gendel, S., Houben, G., Hourihane, J. … Crevel, R. (2009). Approaches to risk assessment in allergy: report from a workshop "Developing a framework for assessing the risk from allergenic foods". *Food and Chemical Toxicology, 47*, 480–489.
Madsen, C. B., Houben, G. F., Hattersley, S., Crevel, R. W. R., Remington, B., & Baumert, J. L. (2014). From Hazard to risk – assessing the risk. Chapter 6. In C. B. Madsen, R. W. R. Crevel, & C. Mills (Eds.), *Risk management for food allergy* (pp. 101–126). Taylor: S.L. Elsevier Inc. ISBN 978-0-12-381988-8.
Nauta, M., Andersen, J. K., Tuominen, P., Ranta, J., & Lindqvist, R. (2015). Risk-based microbiological criteria for Campylobacter in broiler meat: a comparison of two approaches. *Food Control, 53*, 177–184.
Nauta, M. J., Sanaa, M., & Havelaar, A. H. (2012). Risk based microbiological criteria for Campylobacter in broiler meat in the European Union. *International Journal of Food Microbiology, 158*, 209–217.
Norlander, K., Simon, C. M., & Pearson, H. (2010). Hazard v. risk in EU chemical regulation. *European Journal of Risk Regulation, 3*, 239–250.
OECD. (1993). *Safety evaluation of foods produced by modern biotechnology – concepts and principles*. Paris: OECD. Available at: http://dbtbiosafety.nic.in/guideline/OACD/Concepts_and_Principles_1993.pdf.
Qian, H., Chen, M., Kransler, K. M., & Zaleski, R. T. (2014 Apr). Assessment of chemical coexposure patterns based upon phthalate biomonitoring data within the 2007/2008 National health and nutrition examination Survey. *Journal of Exposure Science and Environmental Epidemiology, 23*. http://dx.doi.org/10.1038/jes.2014.24.
Remington, B. C., Baumert, J. L., Marx, D. B., & Taylor, S. L. (2013). Quantitative risk assessment of foods containing peanut advisory labeling. *Food and Chemical Toxicology, 62*, 179–187.
Ropeik, D. P. (2011). Risk perception in toxicology—part I: moving beyond scientific instincts to understand risk perception. *Toxicological Sciences, 121*, 1–6.
Scheer, D., Benighaus, C., Benighaus, L., Renn, O., Gold, S., Röder, B., et al. (2014). The distinction between risk and Hazard: understanding and Use in stakeholder communication. *Risk Analysis, 34*, 1270–1285.
Slovic, P., & Weber, E. U. (2002). *Perception of risk posed by extreme events*. Working Paper. USA and Wissenschaftskolleg zu, Berlin: Columbia University. Available at: https://www.ldeo.columbia.edu/chrr/documents/meetings/roundtable/white_papers/slovic_wp.pdf.
Spanjersberg, M. Q., Knulst, A. C., Kruizinga, A. G., Van Duijn, G., & Houben, G. F. (2010). Concentrations of undeclared allergens in food products can reach levels that are relevant for public health. *Food Additives and Contaminants, Part A: Chem Anal Control Expo Risk Assess, 27*, 169–174.
Spanjersberg, M. Q. I., Kruizinga, A. G., Rennen, M. A. J., & Houben, G. F. (2007). Risk assessment and food allergy: the probabilistic model applied to allergens. *Food and Chemical Toxicology, 45*, 49–54.
Taylor, S. L., Baumert, J. L., Kruizinga, A. G., Remington, B. C., Crevel, R. W., Brooke-Taylor, S. … Houben, G. (2014). Establishment of reference doses for residues of allergenic foods: report of the VITAL expert panel. *Food and Chemical Toxicology, 63*, 9–17.
Taylor, S. L., Houben, G. F., Baumert, J. L., Crevel, R. W. R., Allen, K. J., Dubois, A. … Brooke-Taylor, S. (2015). Understanding food allergen thresholds requires careful analysis of the available clinical data. *Journal of Allergy and Clinical Immunology, 135*, 583–584.
Tice, R. R., Austin, C. P., Kavlock, R. J., & Bucher, J. R. (2013). Improving the human

hazard characterization of chemicals: a Tox21 update. *Environmental Health Perspectives, 121*, 756–765.

Ulbig, E., Hertel, R. F., & Böl, G.-F. (2010). *Evaluation of communication on the differences between "Risk" and "Hazard". Final Report*. Germany: BfR – Federal Institute for Risk Assessment. Available at: http://www.bfr.bund.de/cm/350/evaluation_of_communication_on_the_differences_between_risk_and_hazard.pdf.

UN. (2011). *Globally Harmonized system of classification and labelling (GHS)* (Fourth Revised Edition). ST/SG/AC.10/30/Rev.4. United Nations, New York and Geneva. Available at: http://www.unece.org/fileadmin/DAM/trans/danger/publi/ghs/ghs_rev04/English/ST-SG-AC10-30-Rev4e.pdf.

UNEP. (2013). Rotterdam convention on the prior informed consent procedure for certain hazardous chemicals and pesticides in international trade (Revised in 2013). In *Rotterdam convention secretariat, united nations environmental programme, Geneva, Switzerland*. Available at: http://www.pic.int/TheConvention/Overview/TextoftheConvention/tabid/1048/language/en-US/Default.aspx.

USA. (2004). *Food allergen labeling and consumer Protection act of 2004 (Public law 108-282, title II)*. Available at: http://www.fda.gov/downloads/Food/GuidanceRegulation/UCM179394.pdf.

Vogel, D. (2012). *The Politics of Precaution: Regulating health, safety, and environmental risks in Europe and the United States*. Princeton, New Jersey, USA: Princeton University Press.

WHO. (2008). *Uncertainty and data quality in exposure assessment*. IPCS Harmonization Project Document No. 6. Geneva: World health Organization. Available at: http://www.who.int/ipcs/publications/methods/harmonization/exposure_assessment.pdf.

WHO. (2009). Principles and methods for the risk assessment of chemicals in food. In *Environmental health criteria, 240*. Available at: http://www.who.int/foodsafety/publications/chemical-food/en/.

Wiener, J. B., Rogers, M. D., Hammitt, J. K., & Sand, P. H. (Eds.). (2011). *The Reality of Precaution: Comparing risk regulation in the United States and Europe*. Washington & London: RFF Press.

Wilkinson, C. F., & Killeen, J. C. (1996). A mechanistic interpretation of the oncogenicity of chlorothalonil in rodents and an assessment of human relevance. *Regulatory Toxicology and Pharmacology, 24*, 69–84.

World Food Summit. (1996). *Report of the World Food Summit on 13–17 November 1996*. Rome: Food and Agriculture Organization of the United Nations. Available at: http://www.who.int/trade/glossary/story028/en/.

WTO. (2015). *The WTO agreement on the application of sanitary and phytosanitary measures (SPS agreement)*. Available at: https://www.wto.org/english/docs_e/legal_e/15-sps.pdf.

Wu, F., Groopman, J. D., & Pestka, J. J. (2014). Public health impacts of foodborne mycotoxins. *Annual Review of Food Science and Technology, 5*, 351–372.

Young, S. L., Brelsford, J. W., & Wogalter, M. S. (1990). Judgments of hazard, risk, and danger: do they differ?. In *Proceedings of the human factors society 34th Annual meeting, Santa Monica, CA* (pp. 503–507). Human Factors Society.