New challenges in the risk assessment of chemicals in food

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Abstract

The objective of risk assessment of chemicals in food is to provide the evidence to support protection of consumer health. Some of the key challenges to this objective are financial, or technological, both with respect to innovation in food production and detection of previously unknown chemicals in food. We also need to deal with increasing internet sales and public perceptions that often differ from the expert view.

Financial challenges included the potential for food fraud or deliberate adulteration of foods as unscrupulous producers try to increase their profit margins. In some instances these issues are food fraud and not a food safety concern. However if commodities are not intended for the food chain, then it is necessary to consider possible risks. The challenge is to try to predict future adulterants and to develop new rapid and economical testing methods in the face of reduced capacity for testing of foods at import or on the EU market as a result of austerity measures.

Potential emerging risks include the impact of climate change, which could alter distributions of natural toxins contaminating food, such as mycotoxins, marine biotoxins, and new plant species being introduced to the European Union. We have limited toxicological information on many of these toxins. We need alternative *in vitro* or *in silico* approaches for the risk assessment of individual and multiple toxins and other contaminants in food.

Other challenges relate to developing technologies in the food industry and in other industry sectors if there is a potential for release of novel chemicals to the environment. Efforts to increase economic growth in the EU are encouraging innovation but it is important to ensure that these developments do not compromise food safety.

Many food products are now purchased over the internet, but the quality and safety of the products cannot necessarily be assured, and some are demonstrably harmful.

Finally, with emerging information on multiple chemicals in food in the face of limited resources, we need risk ranking and risk benefit tools to support prioritisation on risks to consumer health in a manner that is risk proportionate without imposing unnecessary burden on food industry (and hence the consumer) or on public funds.

Introduction

The objective of risk assessment of chemicals in food is to provide the evidence to support protection of consumer health. This paper provides a personal perspective of some of the key challenges that the risk assessor faces in order to provide the advice that risk managers require. These have been categorized as factors related to financial influences, the potential impact of climate change, safety of products sold on the internet, and innovation in the industry. There are also specific challenges for toxicologists with relation to developments in toxicity testing and risk assessment.

Financial influences

The past decade has seen a number of high profile incidents in which unscrupulous individuals or organisations introduced fraudulent products onto the market, motivated by the aim for financial gain. The risk assessor needs to determine whether there is a risk to the health of the consumer or the issue is solely one of authenticity.

In 2008, high levels of melamine were found in infant milk and other milk products in China, leading to urinary tract stones in about 300,000 young children and infants and acute renal failure in a small proportion of them. Six deaths were confirmed as related to melamine exposure (Chen, 2009a,b). The method for monitoring protein content of milk was based on total nitrogen content. Therefore it was possible to water down milk to increase profit margins, with addition of the nitrogen-rich chemical melamine to mimic the result for total nitrogen in genuine milk. Fortunately the import into the European Union of milk and infant formula from China is not permitted, but composite products, such as confectionary and biscuits containing Chinese milk powder were on the European market, prompting the need for a rapid risk assessment from the European Food Safety Authority (EFSA, 2008).

More recently, a report by a consumer organisation (Which, 2015) found that one in four samples of dried oregano contained olive and myrtle leaves. Similarly there are reports of low value fish being marketed as higher value products. In these instances a health risk is highly unlikely but the products are fraudulent and misleading for the consumer.

A UK business woman was prosecuted in 2014 for marketing a mixture of shredded polyethylene terephthalate (PET) and powdered brass as an “edible glitter”. PET is considered relatively inert when used as a food contact material such as in food storage containers. Whilst PET itself is of low toxicity, it cannot be assumed that PET glitter particles pass through the gastro-intestinal tract without effect in the body. Because of the small size, they could lodge within the tissues. Due to the relatively large surface area, this could result over time in release of larger amounts of substances from the PET, than occurs when it is in

materials in contact with food. Furthermore, the presence of these particles could result in physical damage to the tissues, but there is a lack of information on the safety or otherwise of these products.

Adulteration of meat products is also common. In many instances this is again an issue of fraud, for example incorporating cheaper meats, but again safety cannot always be assured. A recent example related to the use of horsemeat in products marketed as containing beef in a number of European countries. Horsemeat that is produced as food is a high market product and popular in some cultures. However if horses that were raised for sporting purposes or as companion animals enter the food chain, it is possible that they might contain residues of veterinary medicines not permitted in food animals. A challenge for risk assessors in this type of incident is when these veterinary medicines are not permitted in food animals specifically because of concerns about their toxicological properties. EFSA has produced guidance on methodological principles and scientific methods to be taken into account when establishing Reference Points for Action (RPAs) for non-allowed pharmacologically active substances present in food of animal origin (EFSA, 2013a). This provides an approach to risk assessment for some non-allowed veterinary residues, but specifically excludes substances that cause blood dyscrasias (such as aplastic anaemia) or allergy or are likely to be high potency carcinogens.

A challenge with these types of incident is to try to predict what will be next. The question arises as to whether they are likely to increase with continuing economic recession in some parts of the world, and austerity measures in some Member States having a possible impact of the monitoring of foods entering the EU and on the market. There is a need for new rapid and economical testing methods for food chemicals to support risk assessment and food controls.

Potential impact of climate change

There is much ongoing discussion about climate change and its potential impacts but food safety is sometimes overlooked. One possible impact would be on the profile of fungal contamination of crops during cultivation and storage, with potential for increased exposure to mycotoxins in food. Aflatoxins are highly potent genotoxic carcinogens produced by *Aspergillus flavus* and *A. parasiticus* both pre- and post-harvest. They are especially found in areas with hot, humid climates and are most likely to contaminate tree nuts, ground nuts, figs and other dried fruits, spices, crude vegetable oils, cocoa beans and maize. There are frequent reports of non-compliant commodities imported into the EU. EFSA (2007) concluded that aflatoxins were unlikely to be a major contributor to hepatocellular carcinoma in the EU and that the reduction of total dietary exposure to aflatoxins could be achieved by reducing the number of highly contaminated foods reaching the market and by reducing exposure from food sources forming a major component of the diet. However they also noted that there was

emerging evidence of potential for aflatoxin contamination of feed materials grown in areas of Southern Europe and that it was uncertain whether future changes in climate in the EU would lead to increased aflatoxin contamination (EFSA, 2007).

Within the EU, there appears to have been an increase in cereal crops contaminated with mycotoxins produced by *Fusarium* species as a result of adverse weather conditions at critical periods of the growing season. For example, high levels of deoxynivalenol, zearalenone and fumonisins in maize harvested in 2013 led to a request for a temporary derogation to the mycotoxin regulatory limits in order to prevent disruption in the maize milling chain with serious economic consequences. EFSA (2014) noted that for all three of these toxin groups estimates of chronic exposure exceeded the Tolerable Daily Intakes (TDIs) and the Acute Reference Dose (ARfD) in certain age groups. The requested temporary derogations were estimated to result in only a small increase in the percentages of consumers exceeding the TDIs because of the generally low consumption of maize and maize based products in the EU, compared to other cereal-based products. However, similar problems have affected other cereal crops. In general, temporary derogations leading to short term minor exceedances of a TDI are unlikely to result in adverse effects on health, but exceedance of an ARfD is more of a concern. It should also be noted that zearalenone is a potent oestrogenic substance that could have an impact if exposures are elevated during a critical period of development.

In addition to the currently regulated mycotoxins, a large number of other mycotoxin groups have been identified. For many of these there are limited data on toxicological properties and on the levels present in food. Nevertheless EFSA has identified concerns for several of these, such as genotoxicity and carcinogenicity of citrinin (EFSA, 2012) and sterigmatocystin (EFSA, 2013b) and increased in exposure would be undesirable. The challenge for risk assessment is often the fact that multiple structurally-related toxins can co-occur and there are generally a lack of toxicity data for most of them, particularly with respect to data on relative potency that are required for cumulative risk assessment.

Similarly climate change could result in increased incidences of contamination of shellfish (and finfish) with marine biotoxins in the EU if water temperatures alter (global distribution of marine biotoxins can also be affected by human activity such as shipping). Ciguatoxin (CTX)-group toxins in fish occur in fish as a result of biotransformation of precursor gambiertoxins produced by the benthic dinoflagellate Gambierdiscus toxicus. CTX-group toxins cause ciguatera fish poisoning, which is characterised by a wide variety of symptoms and signs such as gastrointestinal (e.g. vomiting, diarrhoea, nausea), neurological (e.g. tingling, itching) and cardiovascular (e.g. hypotension, bradycardia) effects. They are mainly found in Pacific, Caribbean and Indian Ocean regions and are classified as Pacific (P),

Caribbean (C) and Indian Ocean (I) CTX-group toxins. CTX-group toxins have now been identified for in fish in Europe (EFSA, 2010).

Tetrodotoxin (TTX) is the causative agent responsible for pufferfish/fugu poisoning, which is predominantly found in tropical regions in the organs of fish from the *Tetraodontidae* family, and other marine species such as the blue-ringed octopus and gastropods. The toxin and its structural analogues are thought to originate from a variety of marine bacteria, including *Vibrio* spp. Clinical effects include a range of neuromuscular symptoms such as paraesthesia of lips and tongue, dizziness and headache, together with gastrointestinal symptoms such as nausea, abdominal pain, diarrhoea and vomiting. Higher degree symptoms include ataxia, incoordination, cardiac arrhythmias, seizures and respiratory failure, leading to death. It has recently been reported that TTX is present within the temperate waters of the UK, and has been detected in oysters and mussels (Turner et al., 2015). Higher levels have been reported in mussels harvested in Greek production areas, where it is associated with the presence of *Prorocentrum minimum* (Pavillard) Schiller, a phytoplanctonic dinoflagellate known to cause red tides (Vlamis, 2015).

As with the mycotoxins, marine biotoxins frequently co-occur as multiple related molecules, with limited toxicity data available. The possibilities for generation of new toxicity data are limited by the low amounts or lack of pure toxins available.

Another possible impact of climate change on food safety could be changes in agricultural practice. If there are changes in crop production within the EU, could there be increased pesticide usage such that exposure would exceed the levels predicted during the initial approval process? Similarly, would changes in diseases of livestock alter usage of veterinary medicines? Might there be changes in adventitious weed species, with potential to contaminate the food chain with plant toxins such as tropane alkaloids and pyrrolizidine alkaloids (PAs)?

Although speculative, these questions need to be considered. PAs provide a good example of the challenges to risk assessment. They are biosynthesised by plants as secondary metabolites against herbivores. Approximately 6000 plant species worldwide may contain them, although 95% of PAs are found in five plant families: Asteraceae (Compositae), Boraginaceae, Fabaceae (Leguminosae), Orchidaceae and Apocynaceae. There are more than 600 known PAs, and they have the potential to contaminate honey, salad crops, herbal products, supplements, teas, cereals if grain crops are contaminated with PA-containing plants, and products of animal origin if food-producing animals graze on PA-containing plants or feed contaminated with them. Of the hundreds of PAs identified, relatively few have been tested for in food, and analyses have so far focussed

on a small number of food types (mainly honey and herbal infusions/teas). Therefore dietary exposure estimates are not comprehensive. PAs with a carbon-carbon double bond in the 1,2 position of the molecule, known as the 1,2-unsaturated PAs, are genotoxic and carcinogenic. Very little is known about the toxicological properties of 1,2-saturated PAs. Based on the common mode of action the effects of 1,2-unsaturated PAs are likely to be additive, but the available data are not sufficient to identify relative potency factors. There are insufficient data on levels of PAs in foods. Herbal dietary supplements have the potential to result in the highest exposure and have been known to cause human illness (EFSA, 2011)

Finally, in the context of climate change, there are increasing incidences of severe flooding. This has a potential impact on food chemical safety through redistribution of environmental pollutants such as heavy metals and persistent organic pollutants from industrial sites, or from river sediment onto agricultural land, allotments and private gardens used for growing food.

Internet sales

Internet sales are increasingly popular and this includes food. An area of concern relates to alternative therapies, which some consumers seem to be favouring because of their perceptions that natural is healthy and synthetic is bad, leading them to seek out products marketed as natural. International variations in medicines legislation throughout the EU result in differences in which products are viewed as medicines and which as dietary supplements, and hence a lack of harmonisation in approach to supplements. For herbal products marketed on the internet there is generally insufficient characterization of the content to perform risk assessment and the safety and quality of such products cannot be assured. In contrast there are products marketed on the internet that are definitely harmful. Some internet sites claim that bitter apricot kernels should be incorporated into a healthy balanced diet, that they help reduce pain associated with arthritis, lower blood pressure, and have a role in preventing and treating cancer. These claims have not been substantiated. Bitter apricot kernels contain high concentrations of the cyanogenic glycoside amygdalin, and there are reports of cyanide poisoning, including fatal cases, in the scientific literature. A preparation requiring addition of an organic acid to sodium chlorite is marketed as “miracle mineral supplement” (MMS) or “chlorine dioxide solution” (CDS), with claims that it is a cure for a wide range of diseases and conditions, including malaria, HIV Autoimmune Disease (AIDS), cancer, Ebola virus disease and autism. Acidified sodium chlorite has been used to disinfect water and as a biocide. It is a bleaching agent and has caused damage to those taking it as a supplement. There also seems to be an increasing trend in use of “fat burner supplements” by young people wanting to lose weight or to build up lean body mass. Some of these are herbal preparations for which the quality and safety is unknown, presenting challenges for risk assessment. 2,4-Dinitrophenol (DNP) is also marketed as a fat burner. It is well known in biochemical research as an uncoupler of mitochondrial oxidative phosphorylation, leading to

decreased ATP generation and altered energy metabolism. Indeed, it has previously been investigated as a possible slimming aid, but discontinued due to adverse side effects. Over the past decade there have been reports of young adults having died as a result of taking DNP, although absolute numbers are unclear.

Innovation in industry

Other challenges relate to developing technologies in the food industry – are our current approaches to risk assessment adequate to address engineered nanomaterials released to the environment as contaminants, use of synthetic biology, 3D printing, sensors, intelligent packaging, etc.? Commercial sensitivities can mean that information on new processes is not always readily available to the risk assessor. Similarly, are there developments outside of the food sector with the potential to result in release of chemicals to the environment with potential impact on the food chain? For example, the use of brominated flame retardants (BFRs) has in the past led to release and accumulation in the environment, and some such as the polybrominated biphenyls ((PBBs), polybrominated diphenyl ethers (PBDEs) and hexabromocyclododecane (HBCDD) were subsequently designated as persistent organic pollutants under the Stockholm convention. Especially with the PBDEs, there is concern that dietary exposure could have an impact on human health (EFSA, 2011b). One of the challenges with BFRs is that the composition of the technical mixtures used industrially is not representative of the profile of individual congeners in the food chain, and toxicity data on individual congeners are limited. The banning of some BFRs has led industry to produce alternatives, but so far there is little information on their physicochemical characteristics (which determine persistence in the environment), their toxicity, or their occurrence in environmental media and food, or even on which chemicals are being used (EFSA, 2013c). This is an example of the impact of industrial innovation having an impact on the food chain – there will be others.

Efforts to increase economic growth in the EU are encouraging innovation. There is also increasing focus on securing the adequacy of the food supply. We need to ensure that these developments do not compromise food safety.

Developments in toxicity testing and risk assessment

It is recognized that people are exposed to thousands of chemicals over a lifetime. There are insufficient toxicity data to support risk assessment for many of these chemicals even when considered individually, and insufficient resource to test all chemicals that people are exposed to. Testing for the effects of combined exposures presents even more of a challenge. For some types of chemical, such as natural toxins and components of technical mixtures, the limited amount of material available that can be synthesized or isolated in a pure form presents a barrier to application of current regulatory toxicity protocols. As analytical techniques

improve, an increasing number of chemicals are detected in human blood or urine frequently with associations made to dietary exposure.

Novel approaches to toxicity testing are being developed, such as the Toxicology in the 21st Century (Tox 21) program, which aims to create alternative methods for assessing chemical toxicity that are less expensive and time consuming than conventional approaches[1]. So far these types of approach have found most application in screening, prioritisation of chemicals for further testing, and mechanistic studies particularly in determining whether or not an effect or pathway is relevant to humans. For application in risk assessment the results of *in vitro* or *in silico* studies need to be combined with toxicokinetic modelling to allow assessment of internal or external dose-response relationships. Further development of modelling approaches is required to support approaches not dependent on chemical-specific experimentally generated data.

As noted in many of the examples above, there is a need for risk assessment of combined effects to multiple chemicals rather than simply considering chemicals individually. EFSA has published a number of documents in this area, with particular focus on pesticides. Criteria for grouping active substances into cumulative assessment groups (CAGs) were proposed, based on chemical structure, mechanism of pesticidal action, mode/mechanism of mammalian toxicity and common toxic effects. In particular, it was assumed that mixture effects for substances acting via a common mode of action (MoA) might be predicted by the dose addition (DA) concept. Although the datasets for pesticides are generally much more extensive than for other types of chemicals with the potential to be present in food, EFSA found that mechanistic data to support conclusions on similarity or dissimilarity of mode of action were rarely available. Therefore the recommended approach was to group together all pesticides with common adverse outcomes on the same target organ/system together in a CAG and to assess their combined effects using the concept of dose addition (EFSA, 2013d). This approach means that all pesticides are in a single CAG unless there is a reason to exclude them, i.e. because they do not affect the same target organ/system. Whilst this is arguably reasonable for pesticides because they are designed to be toxic, albeit not to humans, it is not feasible to adopt the same approach to the thousands of chemicals that we are exposed to. Therefore there is a need for criteria for including chemicals in a CAG. Criteria that have been used on an ad hoc basis in defining chemicals to be included in a cumulative risk assessment are based on chemical structure, potential for relevant co-exposure and common mode of action. However potential for relevant co-exposure includes all chemicals that are persistent in the environment and in the human body, and the concept of common mode of action is of limited value given that there are no or insufficient data on mode of action for the vast majority of chemicals.

[1] https://ncats.nih.gov/tox21

The approach to cumulative risk assessment of dioxin-like chemicals, based on the concept of dose addition taking into account relative potencies is an exemplar. It has been applied for over the past three decades, with further refinement in the light of newer research. The criteria for inclusion into the CAG are: similarity of chemical structure; binding to, and elicitation of response via, the Ah receptor; and persistence/accumulation in the food chain (van den Berg et al., 2005). There are few, if any, comparable examples of cumulative risk assessment approaches that are as accepted and applied globally, perhaps because of the vast amount of data required. Again, there is a need for development of predictive models that would allow development of cumulative risk assessments with decreased need for chemical-specific experimental data.

In the future, it can be envisaged that risk assessors will be expected to make use of other types of data, such as greater use of "big data" and information gleaned from social media. How to do this in ways that are transparent and robust will present further challenges.

Concluding remarks

It is anticipated that there will be more instances of food adulteration and fraud. Risk assessment is needed to determine whether there are risks to the consumer, frequently with limited information. Climate change has the potential to alter dietary exposure to natural toxins and to environmental contaminants. Classes of toxins and of environmental contaminants often comprise multiple chemicals, with limited data available to assess toxicity and to support cumulative risk assessment. The safety and quality of substances available on the internet often cannot be assured. Innovation in the food industry and other sectors has the potential to introduce new contaminants into the food chain.

Risk assessment is required for increasing numbers of chemical substances and combinations thereof. Often adequate toxicity data are not available for risk assessment, and there are limited prospects of obtaining more. There is a need for further development of new tools for use in testing and predicting toxicity, and for them to be incorporated into risk assessment approaches. With emerging information on multiple chemicals in food in the face of limited resources, we need risk ranking and risk benefit tools to support prioritisation of risks to consumer health in a manner that is risk proportionate without imposing unnecessary burden on food industry (and hence costs for the consumer) or on public funds.

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