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A framework to determine the effectiveness of dietary exposure mitigation to chemical contaminants

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ABSTRACT

In order to ensure the food safety, risk managers may implement measures to reduce human exposure to contaminants via food consumption. The evaluation of the effect of a measure is often an overlooked step in risk analysis process. The aim of this study was to develop a systematic approach for determining the effectiveness of mitigation measures to reduce dietary exposure to chemical contaminants. Based on expert opinion, a general framework for evaluation of the effectiveness of measures to reduce human exposure to food contaminants was developed. The general outline was refined by application to three different cases: 1) methyl mercury in fish and fish products, 2) deoxynivalenol in cereal grains, and 3) furan in heated products. It was found that many uncertainties and natural variations exist, which make it difficult to assess the impact of the mitigation measure. Whenever possible, quantitative methods should be used to describe the current variation and uncertainty. Additional data should be collected to cover natural variability and reduce uncertainty. For the time being, it is always better for the risk manager to have access to all available information, including an assessment of uncertainty; however, the proposed methodology provides a conceptual framework for addressing these systematically.

1. Introduction

Risk management measures are an important tool in ensuring the safety of food. A variety of approaches can be applied, ranging from consumer advice, codes of practice and, ultimately, regulatory limits for the maximum permitted concentration of chemical contaminants in food. Such measures are intended to reduce consumer exposure to contaminants in the food that may occur either naturally e.g. mycotoxins, result from environmental contamination e.g. heavy metals, or are formed during food processing e.g. acrylamide and furan. The determination of the success of any risk management measure can often be overlooked in the risk analysis process but is as important a step as the risk assessment or the risk management intervention itself. Indeed, the outcome of any risk management measure should feed into a revised risk assessment. Assessing the impact of risk management measures, if done correctly, can lead to more effective risk reduction by identifying measures that are having the biggest impact or no impact at all.

The effectiveness of a risk management measure is typically measured by changes in the intake of a particular contaminant by consumers or certain subgroups within the consumer population which can involve changes in dietary consumption or a reduction in the concentration of a particular contaminant in the foodstuff itself. However, there can be many sources of variation and uncertainty involved – from measuring the chemical contaminant itself to the availability of consumption data – that will have an impact on any conclusions drawn. It is also important to recognise that some individuals will be impacted more than others, and the inter-individual variability must also be considered. These uncertainties should be identified and their impact should be considered in the context of both the exposure assessment and the conclusions drawn on the success of the exposure mitigation measure. It is also becoming evident that some risk management measures can have second-

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ary or unintentional consequences. To include such consequences may require additional consideration and the application of approaches like risk–benefit analysis.

The aim of the current study was to develop a science based approach for determining the effectiveness of mitigation measures on dietary exposure to chemical contaminants in food.

2. Methodology

A general framework for estimating the effectiveness of mitigation measures to reduce human exposure to food contaminants has been developed. The framework was assessed and refined using three different case studies related to certain contaminants in certain food products. The following case studies were chosen so that they cover chemical contaminants having a different nature of occurrence, and the product was deemed very relevant for presence of the particular contaminant: 1) Methyl mercury in fish and fish products, 2) Deoxynivalenol in small grain cereals, and 3) Furan in heat treated foods. Methyl mercury in fish and fish products was selected because of the variation of presence of this contaminant within different species, and the potential high exposure of high fish consumers. The balance of risks and benefits to different sub-populations through their consumption of oily fish is of particular interest, in order to assess what is the best guidance for consumers. Deoxynivalenol in cereal grains was chosen because of the natural occurrence of this contaminant and the large annual variation in the presence and concentrations of this mycotoxin in cereal grains. Furan was chosen because this compound is only formed during heat treatment of food products.

The three case studies have been completed to look at the types of dietary mitigation measures that have been or could be used and the challenges associated with assessing the effectiveness of these measures.

3. Results and discussion

3.1. General framework

The general framework for estimating the effectiveness of mitigation measures to reduce human exposure to food contaminants is presented in Fig. 1. The scheme and results of its application to the three case studies is further detailed in the following sections.

3.1.1. Risk assessment

The basis for any risk management intervention should be a risk assessment demonstrating the need to reduce dietary exposure. The need to reduce dietary exposure may apply across the population or may be targeted at certain population subgroups e.g. pregnant women. The risk assessment may have resulted in a health based guidance value such as a Tolerable Daily Intake (TDI) or, in the case of substances that are both genotoxic and carcinogenic, a margin of exposure (MoE) with – if needed – a recommendation to reduce exposure to as low as reasonably achievable, the so-called ALARA approach. The challenge with ALARA often is in defining what is "reasonably achievable". In preparing the exposure assessment a number of approaches may be used from simple deterministic approaches to more complex probabilistic modelling. If the contaminant of interest is found in several dietary sources then conservative (worst case) intake scenarios may be used or more detailed modelling approaches that give more realistic intake estimates. Any intake assessment has a number of associated uncertainties. The main problem is that the collection of data on food consumption and on the presence of nutrients/contaminants is expensive and, therefore, is often limited. This leads to (sampling) uncertainties, as small datasets are not fully representative of the true distributions (of food consumption and/or contaminant concentrations) of all (sub)populations concerned. Risk is typically associated with intake values occurring in the extreme tails of the distributions. Consumption diaries are often used to capture dietary habits. Typically these diaries cover a short period, e.g. 1–7 days, for around 1000–2000 individuals, but investigations using intake diaries are not regularly updated. Problems can arise when rarely consumed items are of interest, or if more detailed patterns are required such as combinations of foods or consumption amongst specific subpopulations, as these will not be well represented. Assumptions are necessary in practice, such as extrapolating from countries/sub-populations/seasons for which information is available, and assuming typical or average levels for model parameters rather than accounting for the true range of variation. Sampling and measurement uncertainties and simplified model approximations also give rise to uncertainties (Kennedy, 2010). These uncertainties are being made more and more explicit in such assessments (EFSA, 2012a) and must be carefully considered when looking at the impact of any dietary exposure mitigation approach. It is important to consider quantifying the uncertainties in both measured concentrations of the contaminant and consumption data and to generate confidence (or credible) intervals around those exposure estimates. More research is required to quantify complex uncertainties, including the joint distribution of contaminants in cumulative assessments or multivariate modelling of food combinations (Kennedy, 2010). These are relevant for assessing secondary impacts of dietary risk mitigation measures (e.g. likely replacement foods for assessing secondary impacts) but are often unquantified in standard models. The impact of unquantified uncertainties may be evaluated using expert judgement (EFSA, 2006). The same approach should be applied when repeating the intake assessment after the mitigation measures have been applied.

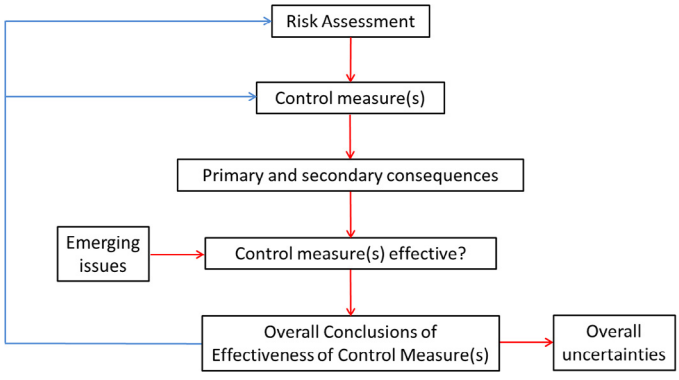

Fig. 1. A stepwise approach to assess the application and impact of any dietary exposure mitigation measure(s) to chemical contaminants in food.

3.1.2. Control measure(s)

The appropriate risk management or dietary intake mitigation measure will be determined based on the occurrence of the contaminant of concern, the processes that lead to its presence in food, and levels of consumption of foods containing the substance. In some cases the measure can be the advice to either the consumer (e.g. in the case of consumption of fish containing methyl mercury), or to growers and processors. For growers and processors this advice may take the form of good agricultural practice or good manufacturing practices. Similarly, toolboxes may be developed containing a number of approaches that can be used to reduce contaminant levels. This approach has been taken for process contaminants such as acrylamide (FoodDrinkEurope, 2014). In some cases, regulatory limits may be put in place to prevent food with high levels of contamination from entering the food chain.

For certain contaminants the goal of the exposure mitigation measure may be clear, e.g. to reduce human exposure below the appropriate health based guidance value such as a TDI. A related goal may be to reduce levels of a contaminant in food to the maximum concentrations specified in legislation. However, for contaminants for which the ALARA approach is used the challenge can be in determining when a reduction in exposure is adequate. The MoE has been developed as a mechanism for prioritising contaminants that require risk management measures and can provide some guidance on when exposure reductions may be considered

adequate. EFSA has advised that contaminants with a MoE of <10,000 are not a priority for action (EFSA, 2012b).

3.1.3. Primary and secondary consequences

The primary or intended consequence of any control measure is to reduce consumer exposure to the contaminant of concern. Some risk management measures are aimed at directly reducing the level of a contaminant in a food, whereas others aim to change consumption behaviour e.g. eating smaller portions or less frequently a certain food item. They may be targeted at certain population groups rather than the entire population, may aim to reduce acute exposure, e.g. from a single serving or portion, or to reduce chronic exposure over time.

Risk management measures could have secondary consequences. Such indirect consequences should be considered before implementing a risk management measure. Could the measure lead to changes in concentrations of other substances in the food which may have harmful or beneficial effects? What could be the impact of changing consumption patterns on the (micro)nutrient intake? Is it likely that consumers may substitute one food with another and what could be the impact of that in terms of nutrient intake? Changes may occur in the organoleptic or aesthetic qualities of a food product as a result of a control measure and this can also impact consumption habits. Answering questions about possible secondary consequences requires a detailed understanding of the total diet across the population and the net health impact of combinations of compounds and potential effects. These are extremely challenging problems, and efforts to address them have been limited so far, e.g. see the Brafo project (Hoekstra et al., 2012), the Qalibra project (Hart et al., 2013) or the Beneris project (Leino et al., 2013). Hart et al. (2013) describe the Qalibra project (Quality of life – integrated benefit and risk analysis) which proposed a general approach to calculate uncertainty and variability in human exposure to various compounds and to characterise the resulting overall health risks and benefits. Aggregation is achieved through the use of the disability adjusted life year (DALY) measure that can combine multiple positive and negative health effects. Qalibra can be used to consider DALYs lost by a population of individuals under a range of hypothetical consumption scenarios.

3.1.4. Control measure effectiveness

An essential part of assessing the impact of mitigation measures to reduce dietary exposure is the collection of appropriate baseline data before the control measure is implemented. However, there may be sources of variation (e.g. temporal or spatial), implying that data need to be collected for several months or years under different conditions and in different regions. Only in this way full insights into the inherent variability in the data can be obtained, allowing a clear assessment of any further steps required to accurately assess the impact of a risk management measure, given this inherent variability. A good example is the mitigation of high mycotoxin concentrations in cereals since these contaminants are known to vary over time and place (see case study). Other sources of variability or uncertainty may exist in sampling strategies used to monitor control options. Careful consideration should be given to these points and appropriate refinements made e.g. targeting relevant foods or regions, or increasing the frequency of sampling or sensitivity of the methodologies used. With limited resources, it is usually not feasible to monitor impacts across all levels of variability. Total diet studies (TDS) provide a practical solution for assessing overall *average* trends in dietary intakes of nutrients and contaminants. For a given country, TDS consider broad food groups separately, e.g. fish, dairy, meat. For each group, TDS involves collecting multiple items from the market, representing the mix of specific foods and amounts generally consumed. Ideally, these are sampled from a range of locations and times of year to account for realistic variation. The collected food items are then prepared and cooked in a standard way and then pooled into single homogenous samples per food group. The aim is to measure average nutrients and contaminant intakes from samples that are typical of the food group for the country, and which accounts for realistic processing effects up to the point of consumption. The pooled samples are analysed, which is more economical and representative for an average intake as consumed. TDS allows for changing dietary and preparation habits, or any other emerging issues, e.g. see Rose et al. (2010). For certain contaminants the sources of uncertainty may be so large when it comes to determining intake via the diet that it may be necessary to consider utilising biomarkers as a more reliable estimate of exposure or obtaining more accurate information before repeating the assessment. For example, detailed consumption data of less-consumed species of fish containing high levels of methyl mercury may not be captured in food consumption surveys, so refined data collection is required.

An important consideration is whether or not the impact of the mitigation strategy can be assessed within the framework of the original risk assessment that gave rise to the need to mitigate in the first place. For example, an exposure assessment may be based on worst-case assumptions using upper percentiles of consumption and chemical occurrence, but the mitigation strategy may be to reduce exposure *on average*. In this case, the reduction in average exposure levels cannot typically be assessed under worst-case assumptions. It may be possible to assume an intake distribution and use the value of the extreme tails, recognising that there would be a level of uncertainty. In some cases it may be challenging to measure the impact of a strategy on exposure within the original risk assessment population/parameters and, therefore, difficult to determine if the exposure mitigation strategy was appropriate to begin with. A significant period of time is usually required before the impact of the dietary mitigation measure can be properly assessed. During that time period new issues or data may emerge, e.g. health based guidance values may be updated or new food consumption surveys may be carried out to reflect changes in food consumption. Additionally, technologies may change or improve e.g. improvement in analytical techniques. More information may emerge on sources of variation in levels of a contaminant. The uncertainties associated with the exposure assessment change as further information emerges. It is important to document and assess any changes in the new exposure assessment and to consider the impact they may have when reaching an overall conclusion on the impact of the exposure mitigation measure.

Sensitivity analysis can be used to consider the impact of mitigation measures, even before they are put in place. The most flexible approach is to employ modelling. As data on actual impacts are almost never available before changes are made, this is usually the only option prior to the mitigation. In a population-based dietary exposure assessment involving multiple foods and over 1,000 consumers, it can be challenging to do a comprehensive global sensitivity analysis because of the high number of inputs. What is typically done is that the drivers of exposure are assessed and relative contributions of different sources considered. This in turn points to strategies for exposure reduction in a quantitative way. Similarly, the model can be run with various 'what-if' configurations to show how hypothetical situations will play out. Examples are used in the Qalibra, Brafo, and Beneris studies cited above. Modelling studies can also be used to investigate which uncertainties have the greatest impact on the result (e.g. as done by Kennedy and Hart (2009), Kennedy (2010), and Slob et al. (2010)). The simplest option is to compare alternative methods, with different uncertainty components included or excluded. Typically before any conclusions can be drawn as to the effectiveness of dietary exposure mitigation measures, a revised risk assessment may be required after the measures have been implemented. New data may have emerged on

the hazard characterisation side and these should be included in the assessment along with the revised exposure assessment. As discussed above it may be possible to use sensitivity analysis to determine what mitigation measures are having the greatest impact and which are having little or no impact. This can inform the next stage of the risk management approach. It is important to include in the conclusions the level of uncertainty associated with the assessment and suggestions for reducing the level of uncertainty.

3.2. Case studies

3.2.1. Methyl mercury in fish and fish products

3.2.1.1. Introduction. Methyl-mercury (MeHg) occurs through natural and anthropogenic processes, and is present in the human diet, mainly in fish and seafood products. Because the compound accumulates in the tissue of fish, concentrations tend to be highest in the larger predatory fish higher up the food chain such as shark, swordfish and tuna. MeHg is a neurotoxin that affects the developing central nervous system in the unborn child. MeHg, as measured in hair, is used as a biomarker for human intake via food, and has been used to link childhood IQ with maternal intake (Cohen et al., 2005).

3.2.1.2. Risk assessment. Published risk assessments and mitigation efforts related to MeHg in the diet have focused on women of childbearing age and the impact on neurodevelopment of the child. Risk assessments are primarily based on epidemiological studies of cohorts, e.g. as held in the Faroe Islands and the Seychelles Child Development Study (Myers et al., 2007). In these studies, biomarkers such as maternal hair are linked with child neurological function/IQ. Associations with cardiovascular disease were addressed by JECFA (FAO/WHO, 2007) and found to be inconclusive.

EFSA (EFSA and Panel on Contaminants in the Food Chain (EFSA, 2011c)) performed an assessment of risk based on data submitted by 4 countries: Germany, Spain, Czech Republic and Slovakia. MeHg was analysed in 1083 samples for the 'Fish and other seafood' FoodEx category. FoodEx is a food classification system developed to allow EU countries to have standardised descriptions of food at different levels of aggregation, from broad categories such as bread, meat, fish, etc. through to individual foods (EFSA, 2011a). Like the earlier JECFA assessment (FAO/WHO, 2007), EFSA (EFSA, 2012a) also reported that evidence for potential health effects, other than neurodevelopmental effects, was inconclusive. A tolerable weekly intake (TWI) of 1.3 μg/kg b.w. MeHg, expressed as mercury, was established by the CONTAM Panel (EFSA, 2012c). This TWI was based on new data on the $BMDL_{05}$ (lower confidence limit of a one-sided 95% confidence limit on the benchmark dose) from the Faroese cohort one at age 7 years. For comparison against this TWI, an assessment of current exposure levels in various population groups was carried out by taking the mean concentration per fish type and averaging the implied intake per person-day using dietary consumption surveys (EFSA, 2011c). Finally, the average daily intake per person was calculated empirically and summaries of the population distributions were investigated for defined sub-populations of interest. This is the observed individual mean (OIM) method for calculating usual intakes. No appreciable differences were found in the intake distribution of women aged 18–45 as compared to the general adult population. A further refinement was made by considering fish consumers only, and taking the 95th percentile intake within each population group. Intake in these groups was found to be highest amongst children, with the dietary exposure of high and frequent consumers varying from a minimum MB (middle bound)[1] of 0.54 μg/kg b.w. per week in elderly to a maximum MB of 7.48 μg/kg b.w. per week in children aged 3–10. The higher exposure in children amongst fish consumers was explained by their higher food consumption in relation to their body weight. The mean dietary exposure was found to be below TWI in all age groups, except in toddlers and children in some surveys. However, the 95th percentile exposures were close to or exceeded the TWI for all age groups. For high consumers of fish meat the TWI may be exceeded by up to approximately six-fold. This group may include pregnant women. The CONTAM Panel also emphasised the need to consider the impact of any control measures on the beneficial effects.

A similar risk assessment was carried out by Zeilmaker et al. (2013) who considered the exposure to MeHg in the Dutch population aged 15 + together with a database of MeHg concentrations of various fish species in the Belgian market (Sioen et al., 2007). This study suggested that consuming 100 g of fish per day would have the greatest impact on reduced IQ of the woman's offspring if the fish was exclusively swordfish, pike, or tuna. For many other fish, this hypothetical scenario would result in a much smaller impact. The study of EFSA (EFSA, 2012c) is more realistic in the sense that it accounts for realistic amounts of each species consumed.

3.2.1.3. Control measures. The main control measure that has been used for methyl mercury is dietary advice aimed specifically at pregnant women in regard to fish consumption. The first ever published advice on MeHg was from the US Environmental Protection Agency (EPA) and Food and Drug Administration (FDA) in 2004. The main recommendations were for pregnant women, nursing women and children to avoid certain species of fish and to restrict consumption to an average of two meals a week of low mercury varieties of fish (US FDA, 2013). The UK NHS website (UK NHS, 2013) says that pregnant women should avoid shark, swordfish, marlin, and also limit the intake of oily fish such as tuna, salmon and trout. The other risks in oily fish are mainly due to pollutants such as PCBs and dioxins. A recent review article by Silbernagel et al. (2011) provides information for physicians on preventing overexposure to MeHg due to fish consumption, and pregnant women or people who consume fish more than once a week are advised to choose low mercury fish species.

In the Qalibra project (Hart et al., 2013), the scenario considered was that all adults would follow a recommendation to consume 200 g of oily fish per week, based on the general advice to consume two portions of oily fish. This was based on the assumption that the beneficial effects from oily fish would generally be at least as important as the risks, so everyone would accept the advice and no individuals would actually reduce their intakes if they were already consuming more than 200 g.

3.2.1.4. Primary and secondary consequences. Data are not always available on the consequences of current advice, so assumptions on these consequences have to be made. The target audience for risk mitigation is pregnant women. If the control measure is advice to minimise consumption of certain fish species then any high consumption amongst this target group should ideally be reduced. The intended primary consequence is therefore a reduction in exposure to MeHg. Ideally, a target reduction in exposure should be

[1] MB here refers to the treatment of concentration measurements found to be below the Limit of Quantification (LOQ) or Limit of Detection (LOD), during the exposure calculation. It is common to find many concentration values <LOD or <LOQ, and alternative methods for dealing with these lead to different results. A simple approach is to replace those values with a lower bound (LB) of zero, and complete the assessment as if those were the observed values. Alternatively, we might replace them by the upper bound UB. For measurements <LOQ this would be LOQ whereas for <LOD it would be LOD. The MB indicates that any missing values were replaced by a mid-point within a region (either 0-LOD or LOD-LOQ, as appropriate).

identified as well as a quantitative assessment of whether adhering to the dietary advice given will achieve this reduction. However, sufficient data on fish consumption by pregnant women is generally not available in national food consumption databases. Some recent cohort studies have been carried out, e.g. by Chan-Hon-Tong et al. (2013). These authors considered information about intakes before and during pregnancy of a range of foods, including fish, and calculated the resulting exposures to MeHg and other compounds. Contamination data in this case came from the French TDS. References are also included to various related studies.

Potential secondary consequences are as follows (more details are given in Hoekstra et al. (2012)):

- Reducing oily fish consumption can reduce exposure to contaminants (MeHg, PCB/dioxins) but also lower the intake of beneficial polyunsaturated fatty acids (PUFAs) such as docosahexaenoic acid 22:6 *n*-3 (DHA). The associated health effects related to reduced oily fish consumption are considered to be: an increased risk of fatal coronary heart disease (CHD), an increased risk of stroke, a change (positive or negative) in IQ of newborns, a reduced risk of low sperm count (infertility) in male offspring, a reduced risk of decreased production of TT4 hormone and diffuse fatty change in the liver. These potential effects have different degrees of evidence based on dose–response or epidemiology data, and occur at different levels of exposure. With this list of potential competing health effects it is possible that the benefits could be reduced in addition to the risks (Hoekstra et al., 2012). It is therefore important to consider the overall net health impact to avoid counterproductive measures being introduced.
- Decreasing fish consumption will probably result into increasing consumption of meat and/or vegetables. There will be associated changes in health risks and benefits from this replacement effect.
- Fish consumption for non-target groups may also be reduced. This may include family members sharing meals or individuals generally following advice not intended for them.

The assessment of Hoekstra et al. (2012) was specifically set up to quantify the overall impact, across the whole population, including multiple risks and benefits. It was assumed that those individuals not within the targeted population and currently consuming more than 200 g oily fish per week would maintain their current level of consumption, to maintain the benefits. The risk assessment was repeated, this time assuming that everyone consuming less than 200 g was to consume exactly 200 g of fish per week, to assess the combined impact on the disability adjusted life years (DALY). In this case, nutrients and contaminants would both be increased for any individual currently consuming less than 200 g/week.

3.2.1.5. Control measure(s) effective. Whether or not the control measure is effective should be assessed by monitoring the consumption amounts and selected fish intake of pregnant women, e.g. using dietary surveys and food frequency questionnaires. For example, Oken et al. (2003) describe the impact on pregnant women's fish consumption following advice to reduce consumption. Additionally, the species of fish being consumed should be examined in detail. Based on an assumed selection of species under the current scenario and hypothetical future scenarios, simple exposure calculations could be performed to update the risk assessment, similar to Zeilmaker et al. (2013). Leino et al. (2013) also consider the net effect of MeHg intake on neurological development, considering three alternative consumption scenarios – regular, lean, or fatty fish consumption – in the Finnish population. Probabilistic modelling was used to account for uncertainty related to contaminant levels, consumption and toxicology variables. Consumption data of 12 commonly consumed fish species were collected from 3827 pregnant women in Finland. Accounting for secondary effects requires a more detailed assessment as performed in Hoekstra et al. (2012), although many simplifying assumptions were necessary in their study to make it practical. Substantial uncertainties remained unquantified.

In 2010, a Joint Expert Consultation convened by the FAO and WHO considered the benefits of DHA versus the risks of MeHg amongst women of childbearing age, pregnant women and nursing mothers, and concluded that – in most circumstances evaluated – fish consumption lowers the risk of suboptimal neurodevelopment in their offspring as compared to not eating fish. Amongst infants, young children and adolescents, the evidence was insufficient to derive a quantitative framework of health risks and benefits (FAO/WHO, 2011).

Overall, to date, no clear conclusions could be drawn – based on the available data – on the effectiveness of the control measures.

3.2.1.6. Uncertainties. The EFSA (EFSA, 2012c) report includes the recommendations of 1) more MeHg concentration data should be obtained in the food groups contributing significantly to exposure, and 2) improved modelling of the dose–response used within the epidemiological studies. The CONTAM panel (EFSA, 2012c) provided the overall assessment that the impact of uncertainties on the risk assessment is considerable but that the assessment is likely to be conservative. The treatment of unquantified uncertainties follows the guidance of the Opinion of the Scientific Committee related to Uncertainties in Dietary Exposure Assessment (EFSA, 2006). The main uncertainties are detailed below:

- Uptake of dietary advice is variable and difficult to quantify, as are the secondary effects linked to replacement food intake and the resulting change in contaminant or beneficial nutrient intakes;
- Similarly, current consumption of fish and the choice of fish species are both uncertain and variable;
- Information underlying the dose–response relationships linking maternal hair/blood to long term MeHg intakes is limited, therefore, the true dose–response is uncertain;
- The level of aggregation in the EFSA comprehensive database does not include detailed information about individual fish species consumed, and in 10 out of 15 surveys there are fewer than 500 women of child bearing age. During pregnancy it is likely that women will reassess their diet, so it is uncertain how accurately the women in these surveys represent the target group of pregnant women;
- MeHg concentration data for individual species are limited and not necessarily representative for a particular country of interest. They originated from both random and targeted sampling, which could lead to overestimation. In addition, the available data were mostly reported as total mercury so a conversion factor had to be assumed;
- Food processing is believed to influence the intake of MeHg, although true cooking practices are variable and the true effects uncertain.

3.2.1.7. Conclusions. This case study illustrates through a review of existing studies, the application of the framework to a situation where a mitigation strategy involves dietary advice based on scientific evidence. Particularly relevant to this example are: the use of modelling studies to investigate alternative hypotheses about actual dietary changes; the impact of potential secondary effects of food substitutions, multiple contaminant and nutrient changes and their health-related consequences. There is evidence to suggest that pregnant women do alter their dietary habits, although the information is not sufficient to determine the extent to which the advice to avoid particular fish species is followed. According to current risk assessments the TWI could be exceeded, particularly for high fish

consumers, but note that the TWI has a built-in safety factor. Beneficial effects of fish consumption and confusion/conflicting information to pregnant women could reduce the effectiveness of the measures (Bloomingdale et al., 2010). However, the advice to avoid particular types of fish is very clear, and the concentration data suggest these fish have substantially higher levels of MeHg.

Many uncertainties exist, making it difficult to assess the impact of the advice. A reduction in these uncertainties and better assessment of the balance between risk and benefits is required before the impact of the advice can be accurately assessed. Quantitative methods, such as those mentioned above, should be employed wherever possible. The dietary intake of pregnant women and other sensitive subgroups should continue to be monitored, and further nutrient and contaminant data should be collected.

3.2.2. Deoxynivalenol in cereal grains

3.2.2.1. Introduction. *Fusarium* fungi are commonly found in the temperate regions of Europe, Asia and America (Parry et al., 1995). Under favourable environmental and agronomical conditions, *Fusarium* fungi may infect cereal grains. Several of the *Fusarium* species are capable, to a variable degree, of producing mycotoxins of the trichothecenes class, such as deoxynivalenol (DON), nivalenol, T-2 toxin and HT-toxin, as well as some other toxins like zearalenone and fumonisins. Due to the large influence of climatic conditions, annual and regional variation in concentrations of mycotoxins in harvested cereals is large. Regulation (EC) No. 1881/2006 sets maximum levels for the presence of DON in European foodstuffs. DON is a chemically stable contaminant, which, to a large extent, survives food processing and occurs in cereal food products.

3.2.2.2. Risk assessment. In the period 1999–2003, the European Commission Scientific Committee for Food adopted a series of opinions on Fusarium mycotoxins, laying down a temporary (t)TDI and then a full TDI for DON of 1 μg/kg body weight (bw)/day, a tTDI of 0.2 μg/kg bw/day for zearalenone, a group TDI of 2 μg/kg bw/day for fumonisins, a tTDI of 0.7 μg/kg bw/day for nivalenol, a combined tTDI of 0.06 μg/kg bw/day for T-2 and HT-2 toxins, and an opinion on trichothecenes as a group (European Commission, 1999, 2000a, 2000b, 2001, 2002a, 2002b, 2002c, 2003). In the framework of Directive 93/5/EEC the Scientific Cooperation (SCOOP) Task 3.2.10 'Collection of occurrence data on Fusarium toxins in food and assessment of dietary intake by the population of EU Member States' was performed and finalised in April 2003 (European Commission, 2003). This SCOOP Task aimed to provide the scientific basis for the evaluation and management of risk to public health arising from dietary exposure to Fusarium toxins, taking into account the most recent data available. During the period March 2002–January 2003, 11 EC Member States provided occurrence data for DON and other Fusarium toxins in cereals and derived products. In total 11,022 samples were analysed for the presence of DON, and in 57% of these samples this toxin was found to be present. For DON most data were available for wheat. The percentage of cereal samples (raw cereals and flours) with a DON concentration of 750 μg/kg or higher was 7%, and the percentage of cereal products with a DON concentration of 500 μg/kg or higher was 6%. Based on deterministic calculations, the average intake level (mean food consumption and mean occurrence data) was low for both the entire population and the group of adults, and did not exceed 46.1% of the TDI of 1 μg/kg bw/day. However, for young children the intake was very close to the TDI. At high intake level (95th percentile food consumption and mean occurrence data) for young children the intake exceeded the TDI and for adolescents (13–18 years old) the intake was close to the TDI. SCOOP stressed the lack of occurrence data, and the lack of harmonised methods for sampling and analysis (which were established later by the EC) and the need for further information on the role of technological processing on the fate of trichothecenes (including DON). To date, no update on the SCOOP risk assessment has been performed. Besides SCOOP, other risk assessments for DON in cereal grains have been performed by JECFA (FAO/WHO, 2011) and by the National Institute for Public Health and the Environment (RIVM) in The Netherlands (2001, 2009), but as SCOOP formed the basis for Regulation (EC) No. 1881/2006, this risk assessment was considered in this study.

3.2.2.3. Control measures. The SCOOP task identified cereals, particularly wheat and maize, as major sources of human dietary intake of Fusarium toxins. The estimated daily intakes of young infants and adolescents were close to or even exceeded the TDI in some cases, like for DON. Based on the SCOOP assessment of the dietary intake and the scientific opinions, the EC set maximum levels for DON, zearalenone and fumonisins, which came into force, respectively, July 2006, March 2007 and October 2007 (European Commission, 2005, 2006b, 2006c). Maximum levels for DON vary between unprocessed, intermediate and finished products, and between product groups, from 1750 μg/kg in unprocessed durum wheat and oats, to 200 μg/kg in processed cereal based foods and baby foods for infants and young children. The aim of the Regulations is to achieve a high level of public health protection by reducing the presence of these mycotoxins in food products to the lowest levels reasonably achievable (ALARA).

Complete elimination of DON and other Fusarium toxins is not possible, therefore, the aim is to prevent and reduce as much as possible their presence in the feed and food chain through Good Agricultural Practices (GAP) in the cereal cultivation stage, and Good Manufacturing Practices (GMP) in consecutive stages of the cereal supply chain. To this end, the EC has published the Recommendation on the prevention and reduction of Fusarium toxins in cereals and cereal products in 2006 (2006/583/EC) (European Commission, 2006a). This recommendation defines general principles for drawing up national codes of practices in member states. The principles refer to factors that can lead to fungal infections, growth and toxin production in cereal crops at the farm level and methods for their control. Factors that are relevant include, amongst others, crop rotation, choice of the variety, crop planning, ploughing and fungicide application (van der Fels-Klerx and Booij, 2010). Farm advice should be given to the growers for proper application of GAP on their farm by farm advisors and consultants. In the UK the authoritative body, the Food Standards Agency, published national codes of practice in 2007 (European Commission, 2006b; UK Food Standards Agency, 2007), at the same time guidelines for growers were published by the UK cereal development board (HGCA, 2010). In member states, national monitoring programmes are in place in order to check compliance to the maximum levels for DON in cereals, as set by the EC. Methods for sampling and chemical analyses are defined by the EC as well (European Commission, 2006d) in order to ensure the quality of the results and for harmonisation of the collected data. Since 2010, EFSA have collated occurrence data for several contaminants including DON from across all member states.

The cereal supply chain often sets lower limits for unprocessed cereals than the EC limits to be sure that processed products comply with EC legislation (van der Fels-Klerx and van Wagenberg, 2014).

3.2.2.4. Primary and secondary consequences. The primary consequence of the control measures is a reduction of the DON concentrations in cereals that enter the food production chain, and thus in food end products. This will directly reduce dietary intake by consumption of cereal derived foods. Through proper application of GAP, DON concentration in the harvested cereals will be reduced. However, due to the climatic and regional influences, a reduction in DON contamination is not guaranteed. Checking of the mycotoxin concentration by chemical analyses is therefore necessary. A critical control point for determining DON concentration is

at mill intake and, depending on the structure of the chain, also at the collector intake (van der Fels-Klerx and van Wagenberg, 2014). At the collector, harvested cereals are collected from a variety of growers. The batches from individual farms are stored into large silos. In the silos, mixing of batches and their DON concentrations occurs. Depending on the country and region, the proportion of the cereal chain that includes a collector stage varies. If a collector is not involved, the miller directly obtains batches of cereals from individual farmers. In that case, the critical control point for determination of DON levels is at the mill. During primary processing (milling), DON concentration of the cereals may be reduced as higher concentrations occur in the outer layers of the cereal grain that forms the bran fraction after milling. Cereal products with a lower bran content than whole wheat (e.g. white flour) have a reduced DON content whilst cereal products with a high bran content (e.g. high fibre breakfast cereals) have an increased DON content compared to the unprocessed wheat. During secondary processing (e.g. baking) DON is highly stable and any reduction achieved is only through the dilution of adding non-cereal ingredients. One possible secondary consequence of the legislation is that secondary processors may reduce the fibre content of products to reduce the DON concentration. This could have a negative effect on health as fibre has an acknowledged health benefit and the European diet is already deficient in fibre (Bates et al., 2010). Another secondary consequence could be the increased usage of fungicides to reduce fungal infection and growth during wheat cultivation, which could result into increased exposure to fungicide residues.

3.2.2.5. Control measure(s) effective. Pieters et al. (2004) calculated human dietary intake of DON by cereal grain consumption in The Netherlands in the periods 1998–1999 and in 2000. The years 1998–1999 showed high contamination of cereal-derived foods with DON and, consequently, measures were taken by the Dutch government and industry, covering prevention of DON contamination of grains and prevention of contaminated grains to be used for consumer products. In the year 2000, DON contamination of wheat was reduced by 50%, and intake of DON via cereal grain consumption by young children was reduced by one-third, as compared to 1998–1999 (Pieters et al., 2004). This might be largely due to sampling and chemical analyses of DON concentration in batches that enter the food chain, and removing contaminated lots from food production. Data on the presence of DON in wheat samples collected at harvest during the 20-year period of 1989–2009 in four northwest European countries showed no significant increase or decrease in the percentage of samples that contained the toxin. However, this percentage seems to increase in the latest study years (van der Fels-Klerx et al., 2012b). Though urinary biomarkers might be used to estimate the effects of the mitigation measures (FAO/WHO, 2012), limited biomarker studies are available and no suitable study was conducted before control measures were introduced to allow an effective comparison to be made post control measures.

3.2.2.6. Emerging issues. Several toxins closely related to DON, including the acetylated derivatives of DON (3- and 15-AcDON), nivalenol and its acetylated derivative, fusarenon X, were not considered in the original risk assessment. The presence of the acetylated DON derivatives seem to be related to the presence of DON (Edwards, 2009b). Zearalenone (ZON) also often co-occurs with DON (van der Fels-Klerx et al., 2012b). Therefore, the control measures aimed to reduce DON are likely to reduce these toxins as well. On the other hand, reducing the presence of DON and ZON producing *Fusarium* species may provide other species the possibility to grow and produce other mycotoxins. The concentration of nivalenol and fusarenon X does not appear to be related to the presence of DON. Furthermore, regression analysis of DON to the type A trichothecenes HT-2 and T-2 in cereals indicate mutual exclusion so when DON concentrations are low, HT-2 and T-2 concentrations are high (Edwards, 2009a, 2009b). Little is known though, on the interacting effects of the complex of *Fusarium* species present on cereals.

A further emerging issue for DON control is the presence of masked mycotoxins. The glucoside metabolite of DON – DON-3-glucopyranoside – occurs in cereals and cereal products, is not detected by standard methods of analysis, and can be metabolised back to the parent mycotoxin molecule by the action of the digestive system. This metabolite, which can be present at concentrations up to 50% of the parent mycotoxin (Berthiller et al., 2009), was not included in the original risk assessment.

3.2.2.7. Uncertainties. Local weather conditions during a short time period of crop flowering have a large influence on *Fusarium* species infection of the crop and mycotoxin production. Modelling studies have shown that seasonal and regional variation can explain to a large extent the variation seen in DON concentration in wheat (Edwards, 2009b). Empirical models to describe DON contamination of harvested wheat in The Netherlands are mostly based on region of the country and rainfall, relative humidity and temperature in different time periods around wheat flowering (Hooker et al., 2002; Franz et al., 2009). Inclusion of the period up to wheat flowering only increased the explained variance of the models a little (van der Fels-Klerx and Booij, 2010; van der Fels-Klerx and van Wagenberg, 2014). The regional variation in DON concentration in a particular cereal cannot solely be explained by the differences in local weather. It is likely that the presence of different fungal species in the *Fusarium* complex may play a role. Furthermore, cereal types and varieties are known to differ in their susceptibility for fungal infection and species involved.

Given the effects of local weather on the presence of *Fusarium* species and their mycotoxins, climate change is expected to influence both the fungi and mycotoxins as well (West et al., 2012). Quantitative data on the impact of climate change is, however, not largely available. Recently, a modelling study estimated the impact of climate change on DON concentration in wheat in north-west Europe in 2040 (van der Fels-Klerx et al., 2012a, 2012c). Results of this study showed no large differences in mean occurrence in DON in the future as compared to the baseline period; however, variation between regions and years was estimated to increase (van der Fels-Klerx et al., 2012c). It is also important to note that the *Fusarium* species complex has continued to evolve over time with changes in the species distribution across Europe having occurred in the last 20 years with the progression of *Fusarium graminearum* into northern Europe (West et al., 2012), which has increased the occurrence of DON in cereals across northern Europe (van der Fels-Klerx, 2013).

Another source of variation is the differences in daily intake of cereal derived products between age groups, between countries, ethnic groups and between groups of consumers, e.g. vegetarians eating more cereal derived foods or celiac patients eating less cereal derived foods. Furthermore, contamination of certain cereal types with mycotoxins may differ amongst regions around the world, for instance, contamination of wheat grown in Ukraine may be different from the same wheat variety cultivated in Scandinavia.

3.2.2.8. Conclusion. Effects of regional and temporal variation, and climate change on the presence of DON, and effects of consumption patterns on the dietary intake of DON, will hinder a proper assessment of the effect of the control measures on reduction of the intake. There is a need for long term data collection to assess the extent of seasonal and regional variation and to accurately quantify chronic exposure. Due to the massive diversity of cereals and sources within the European diet, accurate consumption data is extremely difficult to attain and long-term biomarker studies would better identify the range of acute and chronic exposure to DON. This

should be combined with studies to understand the extent that associated trichothecene mycotoxins and their masked derivatives contribute to the overall toxin load to consumers.

3.2.3. Furan in heat-treated foods

3.2.3.1. Introduction. Furan is the parent compound of a class of compounds known as furan derivatives or substituted furans that are known to contribute to the aroma and flavour of several foods including coffee (Maga and Katz, 1979). But only when its presence was described in canned and jarred foods including baby foods in jars by the US Food and Drug Administration (US FDA, 2004b) furan raised considerable attention and consumer exposure was initially estimated. Following these findings EFSA has published a first 'Report of the Scientific Panel on Contaminants in the Food Chain on furan in food' (EFSA, 2004), concluding "that there is a relatively small difference between possible human exposures and doses in experimental animals that produce carcinogenic effects, probably by a genotoxic mechanism. However, a reliable risk assessment would need further data on both toxicity and exposure". Various programmes and research were initiated to collect data on toxicity, mechanisms of formation and exposure, e.g. EU 6th framework project Furan-RA, http://www.furan-ra.toxi.uni-wuerzburg.de/). Occurrence data were collected by FDA and made publicly available from 2004 through 2008 (US FDA, 2004a). Following up on their report, EFSA has established a monitoring database and regularly published the updated results, providing an updated exposure assessment in the most recent report (EFSA, 2011b).

3.2.3.2. Risk assessment. The first comprehensive risk assessment was only recently published by JECFA (FAO/WHO, 2011), summarising data available worldwide on formation, analytics, levels in foods, exposure assessments, absorption, distribution, metabolism and excretion (ADME), toxicology, carcinogenicity and mechanism of action.

Furan can be formed in foods by thermal degradation processes or the Maillard reaction from a variety of precursors naturally present in foods, such as carbohydrates, amino acids, ascorbic acid or polyunsaturated fatty acids (PUFAs), or through free radical reactions during food irradiation (FAO/WHO, 2011). Because of the conditions of formation (high temperature, closed atmosphere) formation of furan is mostly restricted to industrially heat processed and preserved foods, whilst formation under usual household cooking conditions is much less likely due to fast evaporation of the volatile compound (Crews, 2009).

Human dietary exposure was determined based on occurrence data collected in the European Union (EFSA, 2011c), the US (US FDA, 2007) and a number of national/local surveys. Overall, furan levels were highest for coffee (powder roasted > > instant powder > brewed roasted), baby foods in jars and canned and jarred foods. Publicly available dietary exposure assessments (including worldwide, European and national assessments) were based on deterministic approaches. The exposures reported by JECFA (FAO/WHO, 2011) ranged from 0.25 to 1.17 μg/kg bw/day for adults, from 0.08 to 0.23 μg/kg bw/day for children (1–6 years) and from 0.27 to 1.01 μg/kg bw/day (infants up to 12 months). Highest (95th) percentiles of consumers reached dietary exposures up to 2.22 and 1.34 μg/kg bw/day for adults and infants, respectively. The major contributor to adult exposure was coffee. This is a consistent finding between JECFA (2011), EFSA (2011a) and the various published national Risk Assessment studies (Lachenmeier et al., 2009, 2012; Liu and Tsai, 2010; Mariotti et al., 2013; Minorczyk et al., 2012; Pavesi Arisseto et al., 2010; Scholl et al., 2012a, 2012b, 2013; van der Fels-Klerx et al., 2012b; VKM, 2012; Waizenegger et al., 2012). For children, breakfast cereals are the major dietary contributors to furan exposure. For small infants, the main contributors are baby foods in jars. Pasta, meat and vegetable products were reported to contain considerably more furan than fruit and cereal based products (Jestoi et al., 2009; Lachenmeier et al., 2009, 2012; Pavesi Arisseto et al., 2010; Scholl et al., 2013). Highest exposures were estimated to reach up to 2.8 μg/kg bw/day in this target group (97.5th percentile; Scholl et al., 2013).

Furan is a liver toxin and carcinogen in animal studies and is classified by the International Agency for Research on Cancer (IARC) as 'possibly carcinogenic to humans' (IARC, 1995). Rats and mice given furan orally for 2 years have developed liver tumours (hepatocellular adenoma and carcinoma in rats and mice and cholangiocarcinoma specifically in rats) (US NTP, 1993). The mechanism of action of furan carcinogenicity is unclear, but is supposed to involve the formation of a reactive, ring-opened metabolite, cis-2-butene-1,4-dial (BDA). Genotoxicity cannot currently be excluded, and no safe level of exposure has been established (JECFA, 2011). JECFA applied the MoE approach to furan considering that its carcinogenicity may involve a genotoxic mechanism of action. Benchmark dose modelling was applied to determine the $BMDL_{10}$ of 0.96 mg/kg bw/day based on hepatocellular adenoma and carcinomas developing in mice in a 2-year cancer bioassay (FAO/WHO, 2011; US NTP, 1993). Even though a high incidence of cholangiocarcinomas was observed in rats at the lowest tested dose (2 mg/kg bw/day), the relevance of this endpoint for humans was questioned, since these were only seen in rats and were associated with extreme liver toxicity and an "early and marked biliary tract proliferative response" (FAO/WHO, 2011).

Besides JECFA, a number of other risk assessment studies applied the MoE approach to estimate the level of concern for consumers (including exposures of small children) using either NOAEL, T25 or BMDL10 levels published in the literature as point of departure for the determination of the MoE (Carthew et al., 2010). Resulting MoEs varied strongly depending on the scenarios and conservatism applied and it was more or less unanimously concluded that these MoEs represent a human health concern. Characteristics and results of the individual risk assessment studies are summarised in supplementary materials.

3.2.3.3. Recommendations and control measures. Current recommendations from the published literature, as summarised by the Codex Committee on Contaminants in Food (CCCF) in a Discussion Paper on Furan (Codex Alimentarius, 2011) are mostly directed towards consumers and include e.g. to stay with a healthy and varied diet containing fresh fruits and vegetables, to allow volatilisation of furan by stirring foods in an open pan or preparing food freshly, since cooking at home was found to generate negligible amounts of furan (immediate evaporation). Suggestions have been made that consumers may consider to moderate their coffee consumption or let coffee stand for a few minutes before consuming it. It was concluded that the currently available research was unsuccessful to provide effective solutions for decreasing furan in foods and it was considered premature to establish a Code of Practice (Codex Alimentarius, 2011). However, aforementioned options were suggested as possible consumer education material for national authorities, or for inclusion in a future Code of Practice (Codex Alimentarius, 2011).

Advice to national authorities and food processors is limited to the general recommendation to investigate further into mitigation measures (Codex Alimentarius, 2011). Mitigation strategies proposed in the published literature were reviewed by Anese and Suman (2013). No regulatory limits were established, nor were guidance values or a toolbox approach comparable to the one for acrylamide defined.

3.2.3.4. Primary and secondary consequences of control measures. Since no specific control measures have been put in place, primary and secondary consequences of control measures remain hypotheti-

cal. However, it is conceivable that due to its formation mechanism(s) and suspected precursors, other heat process related contaminants or components might be affected as well by measures taken (Codex Alimentarius, 2011):

- The reactions that generate furan are those that also provide flavour and texture, i.e. organoleptic properties are likely to be affected by any measure. Similarly, microbiological safety or shelf life of canned and jarred food juices may be influenced.
- Furan versus acrylamide formation was studied in coffee under different roasting conditions (Guenther et al., 2010), showing that conditions that lowered furan formation actually promoted formation of acrylamide and vice versa.
- Food components such as PUFAs, ascorbic acid or carotenoids are possible precursors. Avoiding the use or addition of such compounds may change the nutritional profile of some foods.
- If consumers are asked to limit consumption of certain foods, such as coffee, they will likely replace them with other products or beverages (with different or unknown effect/impact).
- Practical aspects and convenience of ready-made food consumption (e.g. outside the home, travelling) may also play a role.

As soon as adverse or beneficial effect data become quantifiable, risk–benefit approaches, such as the methodology developed under the remit of the EU funded project BRAFO (Hoekstra et al., 2012) could be used to determine the effects of control measures.

3.2.3.5. Uncertainties. One of the biggest sources of uncertainty and variability resides in the chemical nature of the volatile furan. Being formed upon heating, it only stays in the product if cooked in closed containers, such as retorting of e.g. pumpkin puree, carrot juices, baby foods in jars (Bianchi et al., 2006; Goldmann et al., 2005; Lachenmeier et al., 2009; Limacher et al., 2008; Wegener and Lopez-Sánchez, 2010) or if trapped in the matrix, e.g., with coffee roasting, grinding, shelf life and preparation (Goldmann et al., 2005; Guenther et al., 2010; La Pera et al., 2009; Mesias and Morales, 2013). Once prepared for consumption, furan was shown to evaporate to different extent (Codex Alimentarius, 2011); however, no quantitative prediction of the loss due to preparation is possible to date. On the other hand, home cooking has shown little potential to generate significant amounts of furan (Crews, 2009).

A validated analytical method to determine furan levels in food is still not available. Recommended analytical methods are gas chromatography-mass spectrometry with headspace extraction or headspace solid-phase microextraction. The FDA published an analytical method, based on headspace sampling followed by gas chromatography/mass spectrometry (GC/MS) analysis, on their website (US FDA, 2006). Analytical methods were reported to be reliable in different matrices and model systems, though sensitive to parameters such as headspace temperature and extreme pH that must be controlled (Altaki et al., 2007, 2009; Crews et al., 2007; Nyman et al., 2006, 2008; Ruiz et al., 2010; Wenzl et al., 2007; Yoshida et al., 2007). No specific analytical procedure was required from member states for the submission of data to the EFSA monitoring database (EFSA, 2010).

Uncertainties in the furan food occurrence database will be generated if information on the sample preparation is not provided with the sample and may thus lead to significant overestimation of exposure. In addition, information on food intake from national surveys or databases may not discriminate canned or jarred versus homemade food consumption, i.e. the food grouping is not appropriate for estimating furan exposure. The furan containing food may be used for the full category (even if other foods in the same category are known not to contain furan), which may lead to additional overestimation of exposure. For instance, JECFA indicated that most coffee samples in the EFSA monitoring database were analysed as instant powder, beans or ground coffee, and not as brews prepared for consumption. Mean furan level for all coffees was then converted to coffee brew by applying a 'universal' dilution factor, disregarding the different types of coffee, and disregarding the potential evaporation upon preparation. Furthermore, furan levels were then assigned to the wider food group, "coffee, tea and cocoa" (FAO/WHO, 2011). A recent study on coffees sold in vending machines showed how furan levels vary not only between vending machines but also over time during the limited short lifetime of a freshly drawn coffee, between vending and consumption, and with or without stirring (Mesias and Morales, 2013).

Besides uncertainties in the food occurrence databases and exposure assessments, uncertainties exist on the toxicological side of the RA. Scientific evidence seems to indicate that a genotoxic mechanism of action for furan carcinogenicity cannot be excluded. Consequently, the MoE approach has been applied to furan in various risk assessment studies. However, dose–response information from animal studies is limited and therefore, different values have been used as the point of departure to estimate the MoE (summarised in supplementary materials). This has been acknowledged as a limitation in the database by JECFA (Carthew et al., 2010; FAO/WHO, 2011).

3.2.3.6. Emerging issues. In order to address uncertainties related to the carcinogenic dose–response (particularly the development of cholangiocarcinomas at low doses), the National Toxicology Program of the US Department of Health and Human Services (US NTP) has recently completed another 2-year cancer bioassay in male rats. The dose range used was 0, 0.02, 0.044, 0.092, 0.2, 0.44, 0.92 and 2.0 mg/kg bw/day. Though the study is completed and histopathology in progress, results are not available yet. The study is expected to improve the dose–response assessment, better define the carcinogenic endpoint and allow refining of the Benchmark Dose estimations (US NTP, 2013).

The current evaluations exclusively addressed furan and its supposed genotoxic metabolite, BDA. However, other similar important flavouring compounds such as the group of alkylated furans potentially share significant similarities with respect to formation, structural characteristics and the resulting potential metabolic fate (EFSA, 2011a; JECFA, 2006; Peterson, 2012; JECFA, 2010; JECFA, 2012). The information database on these compounds is extremely limited regarding both occurrence/exposure and toxicological aspects and, consequently, they have not been addressed in combination with furan. Recent studies indicate that methylfurans may be formed in food in a similar way to furan, i.e. Maillard reactions or thermal oxidation of ascorbic acid (Adams et al., 2011; Becalski et al., 2010; Limacher et al., 2007, 2008). Though levels of 2- and 3-methylfuran determined in a variety of food commodities, including baby foods, were in general lower than those of furan, levels of 2-methylfuran (2-MF) approached those of furan and were even higher in samples of roasted, ground and instant coffees (Becalski et al., 2010). In another study on baby foods, levels of 2-MF and 2,5-dimethylfuran were very close to or even higher than furan (Habibi et al., 2013). The Codex Alimentarius Committee recommended to include "furan analogues that are of toxicological relevance to humans (e.g., 2-methylfuran, 3-methylfuran) in mitigation studies" (Codex Alimentarius, 2011).

3.2.3.7. Conclusions. This case study shows that it can be very challenging to take a compound of recent concern (with ample data available) through the framework. Though many risk assessment studies have identified a potential concern, specific mitigation strategies that could lead to reduction of human exposure have not been formulated to date. A particular problem in the risk assessment is the volatility of furan and the lack of consistent information in the occurrence databases on how samples were generated, on products as purchased from the shelves or as prepared ready for

consumption. This leaves immense uncertainty in the occurrence database and, consequently, any estimated exposure levels. Currently available food intake databases do not allow to reliably estimate furan exposure since the intake of canned or jarred foods may not be specifically recorded. The situation may be better in case of small infants consuming baby foods in jars since their diet is usually less varied than an adult's diet, and child specific intake information is available (e.g. German DONALD study; Lachenmeier et al., 2012).

Current recommendations are directed both to food processors to investigate into mitigation and to consumers related to consumption and cooking habits. Neither a reduction on the occurrence side nor a change in consumer behaviours has been documented to date. Because of these limitations and uncertainties exposure modelling (and modelling of exposure reduction) will be challenging but may be feasible for very specific scenarios. Monitoring of biomarkers of exposure would be an opportunity to relate occurrence and intake data to a more realistic exposure assessment, yet a good biomarker for furan exposure has to be identified.

4. Overall conclusions

Ensuring that mitigation measures put in place to reduce dietary exposure to contaminants are effective is key to reducing consumer risk. In assessing the impact of a mitigation strategy prior to or after its implementation, a risk manager is usually faced with an extremely complex picture. This will typically involve large uncertainties, of many different types, as well as natural variability. It is very important that a risk manager is open about the criteria for success, and can judge these against a risk assessment carried out in a clear and transparent manner. Despite the difficulties, it is always better that the risk manager has access to the relevant information, including an assessment of uncertainty and variability, however large, and the proposed methodology provides a conceptual framework for addressing these systematically. It is then for the risk manager to decide the success of the measures, and act accordingly. Where a quantitative assessment is not possible, or where simple assumptions are necessary, these should be documented.

Transparency document

The Transparency document associated with this article can be found in the online version.

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Appendix: Supplementary material

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