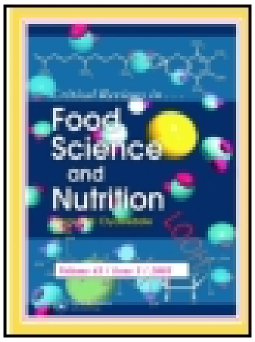
Towards a dietary-exposome assessment of chemicals in food: An update on the chronic health risks for the European consumer



Taylor & Francis
Taylor & Francis Group

Critical Reviews in Food Science and Nutrition

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

Towards a dietary-exposome assessment of chemicals in food: An update on the chronic health risks for the European consumer

Mari Eskola, Christopher T. Elliott, Jana Hajšlová, David Steiner & Rudolf Krska

To cite this article: Mari Eskola, Christopher T. Elliott, Jana Hajšlová, David Steiner & Rudolf Krska (2019): Towards a dietary-exposome assessment of chemicals in food: An update on the chronic health risks for the European consumer, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2019.1612320

To link to this article: https://doi.org/10.1080/10408398.2019.1612320

Published online: 16 May 2019.

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
https://doi.org/10.1080/10408398.2019.1612320

Taylor & Francis
Taylor & Francis Group

REVIEW

OPEN ACCESS Check for updates

Towards a dietary-exposome assessment of chemicals in food: An update on the chronic health risks for the European consumer

Mari Eskola[a], Christopher T. Elliott[b], Jana Hajšlová[c], David Steiner[a], and Rudolf Krska[a,b]

[a]Institute of Bioanalytics and Agro-Metabolomics, Department of Agrobiotechnology (IFA-Tulln), University of Natural Resources and Life Sciences Vienna (BOKU), Tulln, Austria; [b]Institute for Global Food Security, School of Biological Sciences, Queen's University Belfast, Belfast, Northern Ireland, UK; [c]Department of Food Analysis and Nutrition, Faculty of Food and Biochemical Technology, University of Chemistry and Technology, Prague 6, Czech Republic

ABSTRACT

An informed opinion to a hugely important question, whether the food on the Europeans' plate is safe to eat, is provided. Today, the Europeans face food-borne health risks from non-communicable diseases induced by excess body weight, outbreaks caused by pathogens, antimicrobial resistance and exposures to chemical contaminants. In this review, these risks are first put in an order of importance. Then, not only potentially injurious dietary chemicals are discussed but also beneficial factors of the food. This review can be regarded as an attempt towards a dietary-exposome evaluation of the chemicals, the average European adult consumers could chronically expose to during their life-times. Risk ranking reveals that currently the European adults are chronically exposed to a mixture of potentially genotoxic-carcinogenic contaminants, particularly food process contaminants, at the potential risk levels. Furthermore, several of the contaminants whose dietary exposures pose risks appear to be carcinogens operating with a genotoxic mode of action targeting the liver. This suggests that combined health risks from the exposure to a mixture of the chemical contaminants poses a greater potential risk than the risks assessed for single compounds. Over 100 European-level risk assessments are examined. Finally, the importance of a diversified and balanced diet is emphasized.

KEYWORDS
Exposure; risk assessment; contaminants; residues; Europeans

1. Introduction

1.1. Excess body weight – the number-one food-borne public health concern in Europe

Human health is determined by a combination of genetics, physiology, physical environment and food and water safety and quality. The social, economic, cultural and political factors impact these elements having important roles in the overall human health. Presently, the most important food-borne public health concern is excess body weight causally linked to the risks developing non-communicable diseases. These diseases are caused to a large extent by four behavioral risk factors: tobacco use, unhealthy diet, physical inactivity and harmful alcohol use (WHO 2011). Excess weight and physical inactivity increase the risk for cardiovascular diseases, type-2-diabetes and some cancers. These diseases are also inter-linked and diabetes is positively associated with cardiovascular diseases, which were the leading cause of death in the world in 2012 (EFSA 2008a; IARC 2003, 2004; WHO 2002, 2018). According to the World Health Organization (WHO) obesity has nearly tripled since 1975 worldwide (WHO 2011, 2018). In 2014, in the EU nearly 52% of the adults were overweight or obese with rapidly increasing numbers in most of the European countries (Eurostat 2018). Excess body weight is particularly rising amongst children and one third of the European children of 11 years of age are either overweight or obese (WHO Europe 2018). Recently, the European health ministers concluded that increasing obesity in the European children is linked to higher consumption of processed and fast-food, as young consumers eat more often outside of their homes easily accessible food high in fat, sugar and salt (EU Food Policy 2018). Such diets, when consumed regularly, might in a long-term lead to a lowered exposure to vitamins and minerals and cause hidden hunger, as the individual physiological needs for micronutrients are not fulfilled. Obesity is currently responsible for 2–8% of the health costs and 10–13% of deaths in Europe (WHO Europe 2018). In 2004, WHO outlined global actions to support healthy diets and physical activity to tackle overweight and obesity, and in 2007 European Union (EU) presented its strategy to reduce ill-health due to poor nutrition, overweight and obesity (EC

CONTACT Rudolf Krska rudolf.krska@boku.ac.at Institute of Bioanalytics and Agro-Metabolomics, Department of Agrobiotechnology (IFA-Tulln), University of Natural Resources and Life Sciences Vienna (BOKU), Konrad Lorenz Str. 20, Tulln, A-3430, Austria.
This article has been republished with minor changes. These changes do not impact the academic content of the article.

2007). At the national level, European countries have their own actions to promote citizens to consume healthy and balanced diets, and to increase physical activity. The countries provide national dietary recommendations to their citizens, follow their health status and regularly update the guidelines. However, the advice doesn't necessarily capture the attention by all population groups, in particular those individuals with low-income who often encounter many societal difficulties.

The healthy diets can be composed in many ways because of the variety of foods but the principles are generally similar and include eating more fruits, vegetables, legumes, nuts and whole grains, and cutting down on salt, sugar and fats (WHO 2018; Willett et al. 2019). Some EU Member States (EU MSs) limit also trans-fats in certain processed foods, which are also a minute natural component of animal fats. The higher the amounts of trans-fats consumed, the greater the risk is to develop cardiovascular disease (EFSA 2018a). All diet variations have both benefits and potential health risks at the individual and population level (IARC 2003). The effects of a diet with high in fruits, vegetables and whole grains on cancer risk specifically, are considered to be modest, because that type of diet does not appear to be as strongly protective against cancer as it was initially expected (IARC 2014). Overall, body weight management is the key in prevention of all non-communicable diseases including cancer. Currently, discussion on moving nutrition and energy labeling from back to front (front-of-pack labeling) is on-going in Europe to ease the consumers to make informed choices to consume healthy and mindfully. Some countries have also established sugar taxes to contribute to the weight management actions.

1.2. Microbiological food poisoning – the second important food-borne public health concern in Europe

Poisoning from microbiological contamination of the food by pathogens is the second important health hazard for the European consumers. Multiple outbreaks occur annually in the EU making millions of people ill, some resulting in deaths, particularly amongst the most vulnerable in the society. Only in UK over 0.5 million cases due to food borne pathogens was reported in 2009 (Tam et al. 2014). The EU countries have a legal obligation to report food poisoning outbreaks. Over 200 000 food-borne human poisoning outbreaks due to *Campylobacter*, about 90 000 due to *Salmonella* and about 2000 due to *Listaria* are reported annually in the EU (EFSA and ECDC 2017). The annual death rate due to *Listaria* has increased since 2008, with an annual average of nearly 190 persons. In 2016, nearly 250 deaths were recorded and only June-July 2018 nine deaths in five EU MSs (EFSA and ECDC 2018a). In 2016, *Salmonella* outbreaks had the highest number of hospitalizations (1 766 hospitalizations) and deaths (10 deaths). Calicivirus (including norovirus) caused on average the highest number of illnesses per outbreak (32 cases) (EFSA and ECDC 2017). A severe outbreak caused by Shiga toxin-producing *Escherichia coli* occurred in May-July 2011 affecting 4000 people in several EU MSs. Nearly 800 were hospitalized and 53 people died (EFSA 2011a). The presence of antimicrobial resistant bacteria in food can complicate the effective treatment of infectious human diseases and poses probably an even greater threat than microbial food poisoning. Currently in Europe, bacteria from humans and animals continue to show resistance to antimicrobials, even with very high to extremely high resistance, including multi-drug-resistance (EFSA and ECDC 2018b). It is very noteworthy that human consumption of specific antibiotics targeted to multidrug-resistant bacterial infections has almost doubled in Europe between 2010 and 2014 (EC 2018a). WHO has estimated that 25 000 EU-citizens die per year due to the antimicrobial resistance (EC 2018a; WHO 2014). In 2017, a new EU action plan against this exponentially expanding problem replaced the previous one from 2011 (EC 2017a).

1.3. Chemical contaminants in food – the third important food-borne public health concern in Europe

Intentionally used chemicals, which are purposefully present in the foods (e.g. food additives), have been assessed for their safety. Thus, they are not expected to cause human health concerns, provided that the European food law, including the established use levels, is obeyed. Similarly, the safety of intentionally used chemicals but not purposefully present in foods when eaten (residues of pesticides, veterinary medicines and food contact materials) has been assessed. As long as their concentrations are within the legal maximum residue levels allowed to be present in the foods, no health effects are expected. All intentionally used food chemicals require a market authorization in the EU. Unintentionally present chemical contaminants in food, such as environmental and food process contaminants and natural toxins, can pose public health concerns if their concentrations are not kept at appropriately low levels as dictated by legislation. It also appears that the health risks for European citizens from the dietary exposure to certain chemical contaminants cannot be fully avoided even if the regulatory risk management measures are followed. While numerous contaminants potentially harmful to human health are present in food, it is not possible to draw similar estimations for ill-health and deaths for the European citizens in the same way as for food poisoning or antimicrobial resistance. This is mainly due to the fact, that the adverse health effects they may cause are chronic, from the long-term low-level dietary exposures. For some acutely affecting natural toxins (plant and marine biotoxins), human outbreaks from their high dietary exposures have been reported in Europe (EFSA 2008b, 2008c, 2010a, 2013a, 2017a).

1.4. Towards exposome assessment

The dietary-exposome of chemicals can be regarded a part of human exposome concept which considers the total exposure of non-genetic exposures during the human life

(Wild 2012). The human exposome combines the life-time burden of all exposures from external and internal sources taking into account the different natures of the exposures, their changes and the randomness of the events. Human endogenous body functions, such as metabolism, endogenous hormones, oxidative stress, inflammation, gut microflora and aging, form the internal exposure sources, while the large number of external sources are divided into two categories; specific and general external exposures (Wild 2012). The first comprising e.g. dietary, environmental and occupational exposures to chemicals and pathogens, and lifestyle habits (e.g. smoking and alcohol use), and the latter wider social, economic and psychological factors including education, financial status, mental stress, living environment and climate (Wild 2012). Revealing the human exposome would enable the establishment of causality between the development of non-communicable diseases (e.g. cancer) and the combination of external exposures impacted by the endogenous functions and genome (Wild 2012). Omics techniques are seen to be advantageous tools in this work (Wild 2012).

The aim of this review is to provide an informed opinion to the hugely important question, is the food on the Europeans' plate safe to eat? Because the European Food Safety Authority (EFSA) evaluates the risks, the dietary chemicals may pose to the public health in the EU, it was decided that the most appropriate approach was to review the relevant EFSA risk assessments. Therefore, this evaluation is largely based on the available scientific information issued by EFSA. The focus of the review is in the average adult consumer population in Europe. As it often seems that food-borne risks receive more attention than the benefits of food, this review aims at considering them both. Possible impact of climate change, psychological factors (e.g. consumer perception) and food fraud on the dietary exposure to chemicals are discussed. Consequently, this review could be regarded as a first attempt towards a dietary-exposome evaluation of chemicals for the adult European consumers. However, it is limited to those dietary chemicals assessed by EFSA and general knowledge on beneficial substances. For simplicity, the internal exposures from the body functions are omitted and while many external factors are known to influence the dietary-exposome, only some are reflected. Overall, a comprehensive review is presented on the dietary chemicals the average adult European consumers could during their life-times be exposed to, how these exposures could relate to their health and whether they pose potential risks. It should be noted, however, that there are dietary chemicals (such as natural toxins and process contaminants) which have not been assessed by EFSA and whose exposures may also pose risks. Several aspects are discussed, such as dietary habits, exposure to dietary chemicals by different consumers and chemical mixtures. In addition, the risk assessment process and EU-risk management measures are described. As only exposure to unintentionally present chemical contaminants in food may pose health risks, others having been assessed for their safety prior to their authorized use at the regulated levels in foods, the focus of this review is on contaminants. This review considers the exposure only after a legal use of dietary chemicals and possible exposures from illegal use are not taken into account. Similarly, it is considered that the beneficial substances are used within their established dietary reference values to keep their dietary exposures at the appropriate levels. The critical toxicological effects of the chemical contaminants used for assessing the risks and the main sources of the dietary exposures are presented. Furthermore, where risks were identified the used toxicity studies for the critical effects were cited. The review is finished with an attempt to rank the identified risks posed by the chemical contaminants and by considering their combined risks. In this review, 'food' also includes drinks and drinking water.

2. Consumer trust in food safety and consumer perceptions

Consumer trust is important with regard to perception of healthiness of the food. Consumers who have trust in the institutions, who e.g. regulate food applications, see more benefits than risks (Frewer et al. 2011; Hartmann et al. 2018). Although the level of confidence in authorities varies greatly from country to country in the EU, overall it appears that EU-consumers have moderate and similar levels of trust in the EU and national authorities and scientists (ICF and GfK 2018). Only just over half of the EU consumers trust that these actors can guarantee the safety of food. The lowest trust is in the food industry (ICF and GfK 2018), despite the fact that it is the primary responsibility of the food and feed business operators that food is safe and compliant with the law (EP and Council 2002). Consumers have different educational backgrounds, perceptions and interests. Psychological factors, consumer attitudes and emotional affect can impact consumers' healthiness evaluations. For example, it appears that consumers without having been medically diagnosed with celiac disease consider gluten-free products healthier than the gluten-foods (Hartmann et al. 2018). By law, the food is unsafe if it is *"injurious to health or unfit for human consumption"* (EP and Council 2002). The EU-consumer perceptions of the unsafe food appear to focus on acute microbiological outbreaks and concerns of the use of veterinary medicines, including antimicrobial resistance (McEvoy 2016). It also seems that the consumers associate chemicals in food with food additives and other intentionally used chemicals rather than with chemical contaminants (FSA 2017). Consumers appear to have a low awareness and understanding of chemical contaminants, which are typically seen resulting from industrial processes and human error (FSA 2017). The EU-consumers tend to be more worried about the established risks, such as pathogenic food poisoning, than possible emerging risks. From the emerging risks, food fraud is the greatest concern (ICF and GfK 2018). As many societal, cultural and historical factors impact the consumer perception on food-borne risks, the effective communication about the food safety has become challenging (Frewer et al. 2016; ICF and GfK 2018). In the same context, the necessary information needs to be appropriately provided while not unduly worrying consumers. Therefore, while communicating risks, the established risk management measures are important to be conveyed (Frewer et al. 2016; FSA 2017).

2.1. Food-crisis situations can impact dietary exposure to chemicals

The food-crisis situations of the mad-cow disease and Belgian dioxin scandal in the 90's promoted the establishment of the current EU food safety system in 2002. Later, a few situations of foods accidentally contaminated with chemicals; dioxins in pork and nicotine in wild mushrooms (EFSA 2009a, 2009b), could have escalated to the European-wide crises. More complex situations rise from illegally used chemicals in the food production and food-fraud. In 2017, eggs contaminated with an illegal veterinary medicine (fipronil) expanded to the other EU MSs from Belgium (EFSA 2018b). In the horse meat food-fraud in 2013, where beef was replaced by horse meat in many products, an illegal veterinary medicine (phenylbutazone) was detected in horse meat across the EU. A low risk from its exposure was concluded and new risk management measures were introduced (EC 2018b; EFSA 2013b; McEvoy 2016). The Chinese large-scale protein fraud, where melamine and cyanuric acid were added to infant milk powder and other milk products to trick protein analysis, reached Europe in 2008 when the Chinese foods containing milk powder entered to the EU (EFSA 2008d). The exposure to melamine in these products did not pose potential risks, except for some children (EFSA 2008d). The import of Chinese milk products to the EU was banned (EC 2017b; EFSA 2008d). In the same year, another potential crisis situation due to mineral oil presence in imported sunflower oil took place, but did not cause risks (EFSA 2008e). Clearly, illegal use of chemicals or food fraud should not happen, but they have occurred and it is naive to think they will not occur again. The food crisis events lower consumer trust in food safety and can increase the potential risks from the exposure to substances not subject to the regular control. To mitigate this, an EC food fraud center was established and Europol cooperates with the EU Food Fraud Network (EC 2018c).

3. Daily food is a complex mixture of beneficial and harmful chemicals

Food is a complex mixture of a large variety of chemical substances. It contains beneficial substances (e.g. macronutrients and micronutrients) and potentially hazardous chemicals. While many of the macronutrients, micronutrients and water are natural chemical constituents of the foods, several chemicals have been added intentionally, such as food additives and nutritional supplements (e.g. vitamins, minerals and fiber). For the purpose of food adulteration, illegal substances have also been added intentionally, but for the purpose of economic gain. Many chemicals are permitted to be used during food production, but are not intended to be present in the food during consumption. These include residues from plant protection products (pesticides), veterinary medicinal products and food contact materials. A large amount of chemicals present in food, are there without any useful purpose and present unintentionally; these are the environmental pollutants and contaminants that derive from food processing and packaging. Many chemicals occur naturally in the environment whose presence in the food is without an intended purpose, but due to their natural occurrence are unavoidably present. These are endogenous chemicals, such as plant toxins and natural food constituents like nitrate and caffeine, and exogenous chemicals, such as mycotoxins and marine biotoxins.

The potential risks from the most important dietary contaminants to the public health are managed with various regulatory measures, including EU maximum levels (EU MLs) and monitoring (EC 2006a, 2006b, 2013, 2016, 2017c, 2017d, 2018d; EP and Council 2004) as well as providing consumer advice at the EU MS level. The EU food legislation stipulates that food containing a contaminant in an amount unacceptable for public health shall not be placed on the market, that contaminant levels should be kept as low as can reasonably be achieved and that, if necessary, the European Commission may establish maximum levels for specific contaminants (Council 1993). The EU MLs for contaminants have been established for the foods consumed regularly, those which are particularly susceptible for contamination, and for foods for infants and small children. For example, heavy metals, dioxins and polychlorinated biphenyls (PCBs), polycyclic aromatic hydrocarbons (PAHs), 3-monochloropropane-1,2-diol (3-MCPD), glycidyl esters, nitrate, mycotoxins, marine biotoxins, tropane alkaloids, erucic acid and melamine have the established EU MLs (EC 2006a, 2016, 2018d; EP and Council 2004). In certain cases, the food contaminant falls under several EU-regulations such as melamine and mineral oil hydrocarbons. The use of latter is stipulated by the EU-regulations on food contact materials, food additives and pesticides. Other regulatory risk management measures are also in place, such as strategies to mitigate the levels of mycotoxins in cereals and formation of acrylamide in food processing or the EU-benchmark levels for acrylamide and guidance levels for T-2 and HT-2 toxins (EC 2006b, 2013, 2017c). In 2017, a recommendation to monitor mineral oil hydrocarbons in food and food contact materials was introduced by the EU (EC 2017d). The EU MSs have obligations to enforce the measures and perform official controls to ensure that the levels of contaminants in foods are below the regulatory levels.

While some chemical contaminants have been regulated in the EU for a long time, such as nitrate since 1997 and aflatoxin 1998, others e.g. perfluoroalkylated substances (PFAS), brominated flame retardants (BFRs) and certain mycotoxins, have not been regulated. For many of these, more monitoring and toxicity data are required prior to establishment of accurate and proportionate risk management measures. However, even if the data have uncertainties the EU-level precautionary measures can be applied for the contaminants to protect public health. Where the EU-wide legislation is not in place, the national EU-country specific legislation is used. In addition, the national food safety agencies provide consumer advice. For example, as a large variety of fish species with highly variable methylmercury levels are consumed in Europe, the consumers are provided advice on fish consumption at the national level. National authorities similarly advice consumers on the cooking methods to decrease the PAHs and acrylamide exposures, and on the importance of diversified and balanced diets to keep the dietary exposures to the chemical contaminants at the appropriately low levels. For example, national food safety agencies of France and Ireland provide a consumer advise on diversified and balance diets (ANSES 2016; FSAI 2019) as does also EFSA (EFSA 2019a).

3.1. Exposure to hazardous chemicals may pose health risks

Hazardous chemicals have intrinsic toxic properties which potentially can harm human health. While they can induce toxic effects, such as carcinogenic, hepato- and neurotoxic effects, these chemicals have different toxicological potencies with some being much more potent than others. A single chemical can also represent multiple hazards (e.g. it could be a reproductive toxicant and a carcinogen) (IPCS 2009). A hazard is defined as 'a biological, chemical or physical agent in, or condition of, food with the potential to cause an adverse health effect' by EP and Council (2002). The hazardous substance may only adversely impact health when human is exposed to it at the dose levels which are high enough to cause adverse effects (IPCS 2009). However, even after the exposure at the levels observed adversely impacting health, the many biological mechanisms in a human body can counteract the adverse effect and reverse it (IARC 2008). Thus, not all exposed people develop negative health consequences. Risk is defined as 'a function of the probability of an adverse health effect and the severity of that effect, consequential to a hazard' (EP and Council 2002). Thus, risk is a likelihood and therefore a term a potential risk is used. However, for some chemicals it is not possible to identify an exposure level without a potential risk (IPCS 2009). These are typically chemicals directly reacting with human genome (DNA) but also some chemicals inducing e.g. neurobehavioral effects or aplastic anemia.

Cancer is a highly complex disease, which development requires a damage in the DNA (IARC 2008). Depending on the exposed substance, either DNA-reactive or less toxic metabolites can be formed leading to an increased or decreased cancer risk (IARC 2003). It is thought that the genotoxicity may be formed by either direct or indirect biochemical mechanisms operated by the substance (EFSA 2009c, 2009d; IARC 2003, 2008). In the direct mechanism, the genotoxicity occurs because of the direct modification of the DNA by the substance (e.g. by forming adducts with the DNA). This is believed to be without a threshold dose. In the indirect mechanism, the substance does not react directly with the DNA but modifies it or chromosomes in other way (e.g. by production of oxidative stress leading to the generation of reactive oxygen species which could then modify the DNA). These processes are believed to have a threshold dose. Even under normal cellular conditions the human DNA encounters damages from continuous exposure to endogenous and exogenous genotoxic substances (IARC 2003, 2008). They are repaired by many biochemical mechanisms but cancer may develop if they fail (IARC 2008). Carcinogenicity of the substances is classified based on the strength of the evidence on their carcinogenicity in humans, not the carcinogenic potency of the substance (see e.g. IARC 2018). The group 1 substances ('carcinogenic to humans') have the most sufficient evidence on carcinogenicity. For the International Agency for Research on Cancer (IARC) classifications only the hazards are evaluated but the exposures to them are not calculated, and therefore the potential risks are not assessed.

3.2. Risk assessment of chemicals in food

Risk assessments are typically based on a large body of publications identified in an extensive literature searches or using the principles of systematic literature review. This can result in hundreds or even thousands of scientific papers which are evaluated in detail by the scientists of the risk assessment body and who write the scientific risk assessment. Therefore, a final risk assessment can contain from about hundred to several hundreds of citations of the original scientific studies. As development of a risk assessment requires expertise from different scientific fields, such as toxicology (e.g. toxicokinetics, carcinogenicity, genotoxicity, developmental and reproductive toxicity, hepatotoxicity, nephrotoxicity, endocrine disruption, immunotoxicity, neurotoxicity and epidemiology), chemistry, analytical methods, dietary exposure and statistical modeling, a group of scientists jointly writes the risk assessment, each contributing with their fields of expertise (Eskola et al. 2018; IPCS 2009). The risk assessment principle is that the assessment is based on a weight of evidence of the data from all available scientific studies evaluated by the scientists. For the chemical risk assessment, toxicity assessment (hazard identification and characterisation) and exposure assessment are performed. Their outcomes are compared to characterize the risk, and the uncertainties of the assessment are described and, if possible, quantified (Benford 2017; EFSA 2018c; Eskola et al. 2018; IPCS 2009; Yoe 2012). The toxicity assessment evaluates a weight of evidence of toxicological data for adverse health effects, describes a relationship between the exposure (dose) and response of the effect, and identifies a critical effect (IPCS 2009). It is the adverse effect at the lowest dose of all relevant effects observed. When this critical effect is assumed to have a threshold dose, a health-based guidance value (HBGV), such as tolerable daily intake, is derived. At this level human exposure is considered to be without appreciable health risk. In the derivation of the HBGV, the uncertainty factors to account for inter-species and inter-individual differences and the additional uncertainty factors to account for the deficiencies in the toxicity database are taken into account (IPCS 2009). For genotoxic-carcinogens, the assumption is that there is no a threshold dose and that at any exposure level some degree of risk exists (IPCS 2009). For these chemicals, a benchmark dose modeling is used to calculate the reference dose (benchmark dose limit (BMDL). To assess a dietary exposure, food consumption and occurrence data are combined by mathematical methods (IPCS 2009). Either chronic or acute exposures or both, depending on the toxic effects, are estimated. Food consumption data collected by dietary surveys reflect what individual consumers or groups consume (IARC 2018; IPCS 2009). Occurrence data with a low amount of left-censored data (data below detection limits) lower the uncertainty of the exposure assessment (IPCS 2009), and therefore sensitive techniques, such as liquid chromatography-tandem mass spectrometry, are commonly employed. Occurrence data from surveys are most commonly used to calculate the exposure, while concentrations from total diet studies (TDSs) provide data measured in foods as consumed (ANSES 2011, 2016; IPCS 2009). The exposure exceeding the HBGV indicates a potential risk (IPCS 2009). For the chemicals without threshold dose or when the toxicity database is weak, a margin of exposure (MOE) approach is used to characterize the risk by comparing the exposure to the BMDL (IPCS 2009). The MOE of 10 000 or higher implies that the exposure to the chemicals without a threshold dose poses a low risk (EFSA 2005a).

3.3. Consumers are exposed to mixtures of dietary chemicals with variable levels

What the consumers eat and how much depends on individual needs (e.g. age, gender, physical activity and lifestyle), cultural background, availability of the foods and dietary habits. Since the foods included in the daily diets are highly versatile, the exposures to different food chemicals vary greatly. On each day, the consumers are exposed to a large mixture of beneficial chemicals and chemicals intentionally and unintentionally present in the foods. The levels of chemicals are highly variable from effectively zero (i.e. below the detection limit) up to high concentrations. In Europe, the main contributing factor to the exposure levels of the contaminants is usually the amount of consumed food rather than the chemical contamination, because the levels are normally low. The amounts of consumed foods vary greatly. For example, some people are high consumers of fish and seafood, while others do never eat them. The high European fish consumer (four servings per week) is exposed to high levels of beneficial chemicals in fish, but simultaneously also to high levels of certain contaminants, such as methylmercury (EFSA 2015a). However, even the high fish consumers do not continuously eat the same fish species, and because the different fish species are contaminated with different chemicals at the variable levels, the exposure fluctuates over the time.

Children's dietary exposure is typically the highest (2–3 times greater than adults), largely due to their higher food consumption relative to the body weight (EFSA 2006a, 2011b, 2017b; WHO 2006). They are a vulnerable consumer group, not only because of their sensitivity due to the development and maturation of the organ systems, but also due to their early stage of life having future years to develop a chronic illness (EFSA 2017b; WHO 2006).

The entire amount of the chemical, which the consumer has been exposed to, is not necessarily bioavailable to the body. This, because the bioavailability depends on the chemical, dose and diet. Before any chemical can induce any positive or negative effect, it needs to be absorbed from the gastrointestinal tract and cause systemic (internal) exposure in the body. For example, nearly all ingested inorganic arsenic or acrylamide are absorbed in humans, while 50% of ingested tetrachlorodibenzodioxin (TCDD) and only about 5% of fumonisin B1 are absorbed (EFSA 2009c, 2015b, 2015c, 2018d). After absorption, the chemical is distributed to the organs, metabolized and excreted depending on its toxicokinetics and dose. Inorganic arsenic, acrylamide and fumonisin B1 are readily excreted approximately within a day with no accumulation, but dioxins (such as TCDD) accumulate in the body (EFSA 2009c, 2015b, 2015c, 2018d).

Expose to the chemical mixtures may result in combined effects; additive, synergistic or antagonistic (Kortenkamp et al. 2009). The manifested effects depend on the toxic properties of the different chemicals, the composite of the mixture with these chemicals and their doses over the time (EFSA 2018e, 2018f, 2019b, 2019c). As the combinations of these factors are numberless, the risks from the chemical mixtures are difficult to assess and only recently instructions, including for mixtures with chemicals of dissimilar mode of action and genotoxic carcinogens, were given (EFSA 2018e, 2018f, 2019b, 2019c).

4. Risks from the exposure to chemical food contaminants in a spotlight

4.1. Environmental chemical contaminants

4.1.1. Heavy metals and other metals

Mercury, lead, cadmium and arsenic are environmental contaminants that are found in nature, both from natural occurrence and from anthropogenic activity (EFSA 2009c, 2009d, 2010b, 2012a). Nickel and chromium are other widespread metals in the environment due to their natural presence and human activity (EFSA 2014a, 2015d).

4.1.1.1. Lead, cadmium and arsenic. At the current levels of chronic dietary exposures, cadmium, arsenic and lead pose a potential health risk for some average adult Europeans, children having even higher risks (EFSA 2009c, 2009d, 2010b). Many plant-based foods and tap water make the greatest contributions to the Europeans' exposure to lead. Epidemiological evidence shows that a chronic exposure to lead induces cardiovascular effects and kidney disease in adults (Navas-Acien et al. 2009; Selmer et al. 2000). In pregnant women, exposure may cause negative effects on neurodevelopment in the new-borns (EFSA, 2010b; Lanphear et al. 2005). Plant- and meat-based foods are the most important sources of the dietary cadmium. Particularly high bioaccumulation of cadmium occurs in rice (EFSA, 2010b). Smoking is an important non-dietary source for cadmium (EFSA 2009d). It accumulates in the kidney inducing renal dysfunction and cause bone demineralization (Åkesson et al. 2006; Alfvén et al. 2000, 2004; Amzal et al. 2009; EFSA 2009d; Gallagher et al. 2008; Jin et al. 2004; Schutte et al. 2008; Staessen et al. 1999; Wang et al. 2003). IARC has classified cadmium as a 'carcinogenic to humans' (group 1) but it is not directly DNA-reactive (EFSA 2009d). Cadmium acts as a carcinogen after inhalation but not after oral exposure. Inorganic forms of arsenic (e.g. arsenic III and V) are much more toxic than many of its organic forms (e.g. arsenobetaine, arsenocholine and arsenosurgars). In seafood most of the arsenic is organic, while the inorganic arsenic bioaccumulates in rice and marine algae. Washing rice before cooking and discarding the cooking water can reduce its levels (EFSA 2009c). The main sources of the Europeans' dietary inorganic arsenic are dairy and cereal-based products (EFSA 2009c, 2014b). The human data show that its exposure can cause lung, urinary bladder and skin cancers and skin lesions (Ahsan et al. 2006; Chiou et al. 2001; EFSA 2009c; Ferreccio et al. 2000; Karagas et al. 2002, 2004; Xia et al. 2009). IARC has classified inorganic arsenic as a 'carcinogenic to humans' (group 1) but it appears not to be directly genotoxic (EFSA 2009c).

4.1.1.2. Mercury and methylmercury. Chronic dietary exposures to mercury and to its most important dietary form, methylmercury, do not pose a risk for the European consumers, unless large amounts of fish and fish-products are frequently consumed (EFSA 2012a). In particular, predatory fish and old fish have high mercury levels. Methylmercury exposure has been associated with neurodevelopmental effects in humans and cardiovascular effects are also of potential importance in humans (EFSA 2012a, 2014c, 2015a).

4.1.1.3. Nickel and chromium. The current level of chronic nickel exposure is a potential risk for the average consumers in Europe at all ages, the main sources including plant-based foods and nonalcoholic beverages (EFSA 2015d). The exposure to nickel exerts reproductive and developmental effects in animals and it has been classified as a 'carcinogenic to humans' (group 1) by IARC, but it is likely not directly DNA-reactive (EFSA 2015d; SLI 2000a, 2000b). After an oral exposure, nickel appears not to act as a carcinogen (EFSA 2015d). While the chronic dietary exposure to the lowly toxic trivalent chromium it not a risk, the exposure to the genotoxic-carcinogenic hexavalent chromium poses a low potential risk for the Europeans (EFSA 2014a). The hexavalent chromium appears driven by exposures from drinking water and drinks made in drinking water. For the exposure of the trivalent form, vegetable-based foods and food supplements (due to the permitted use) make the greatest contribution (EFSA 2014a). Hexavalent chromium causes different types of cancer by directly reacting with DNA and bears the IARC classification of 'carcinogenic to humans' (group 1) (EFSA 2014a; NTP 2010).

4.1.2. Persistent organic compounds

Persistent organic pollutants (POPs) are halogenated organic compounds that remain intact in the environment for years. Most of them are man-made but some may also form naturally. Exposures among human populations are common since: numerous POPs were (and several remain) widely used, they have dispersed due to global long-range transport, and they bioaccumulate in fatty tissues (particularly those in fish and animals). Their exposure may cause cancer, allergies, reproductive disorders, and disrupt the nervous and immune systems. Some POPs are endocrine disrupters (CHM 2018). Use of many pesticides considered as POPs were banned in the EU in the 70's. The EU continues to regulate POPs jointly with the international Stockholm Convention cooperation (CHM 2018). Certain dioxins, brominated flame retardants (BFRs) and perfluoroalkylated substances (PFAS) are regarded as POPs. PAHs, which contain only carbon and hydrogen, are also persistent substances in nature, but not listed as POPs (CHM 2018).

4.1.2.1. Dioxins, dioxin-like and non-dioxin-like PCBs. Dioxins are a large group of persistent organochlorine substances, with no technological or other use, formed during burning or as unintentional by-products of industrial processes (EFSA 2015c, 2018g). Two large groups of tricyclic chemicals, polychlorinated dibenzo-p-dioxins (PCDDs) and dibenzofurans (PCDFs), are considered together as 'dioxins'. Seventeen of them pose health concerns with highly variable toxic potencies (EFSA 2015c, 2018g). Human studies show that male reproductive effects (impaired sperm quality) are the most critical after the dioxins exposure (EFSA 2018g; Mínguez-Alarcón et al. 2017). IARC has classified TCDD, one of the most potent and studied dioxins, as 'carcinogenic to humans' (group 1) but it is not directly DNA-reactive (EFSA 2018g; JECFA 2002). Twelve of the about 200 PCBs have similar biological activity to dioxins and are therefore referred as dioxin-like PCBs (dl-PCBs). The rest are non-dl-PCBs and not exhibiting dioxin-like activity. Their exposure may cause adverse effects in liver and thyroid. PCBs, some highly persistent in nature, were extensively manufactured for the industrial usages, but from the 70's this was discontinued (EFSA 2005b, 2011c, 2015c, 2018g; JECFA 2016). Dioxins and PCBs occur in complex mixtures and due to their ubiquitous presence, all people have background exposure (EFSA 2018g; JECFA 2016). In Europe, over the last three decades, the dietary exposure to dioxins and PCBs has declined. In the recent past 10 years the decrease to dioxins and dl-PCBs was from 16% to 79% for the average consumers (EFSA 2012b, 2015c). Nevertheless, the average adult consumers are presently still at the potential risk caused by the dioxin and dl-PCB dietary exposures, children having even a greater potential risk (EFSA 2018g). Due to the reduced exposures to non-dl-PCBs, they unlikely pose a risk (EFSA 2012b; JECFA 2016). For adults, fish and sea food are the main contributing foods to the dietary exposure but also cheese and meat-based foods contribute (EFSA 2018g). Finland, Sweden and Latvia have a derogation from the EU MLs for dioxins and allow certain fish species exceeding the MLs to be consumed by their citizens. This due to the recognized dietary benefits of fish consumption.

4.1.2.2. PAHs, BFRs and PFAS. In complex mixtures occurring PAHs are persistent organic chemicals that are formed unintentionally during incomplete combustion of organic matter, various industrial processes and thermal food processing. Currently, the chronic dietary exposure to PAHs poses a low potential risk for the average European adult consumers (EFSA 2008f; JECFA 2006). Fishery products and cereal-based foods are the greatest contributors to their exposure (EFSA 2008f). Smoking is an important non-dietary source. Prevention of fat from dropping into the heat source, and not burning the food, reduce the PAHs levels. Derogation from the EU MLs is applied for many European countries who then can sell on their national markets traditionally smoked products at the higher PAHs levels. Several PAHs are genotoxic carcinogens forming directly adducts with DNA in animals (Culp et al. 1998; EFSA 2008f; Schneider et al. 2002). IARC has classified the most studied PAH, banzo[*a*]byrene, as 'carcinogenic to humans' (group 1) and several others as 'probably carcinogenic to humans' (group 2A) (IARC 2010a, 2012). BFRs are complex organobromine mixtures of industrial chemicals that are added to various consumables and equipment to make them less flammable. The use of certain BFRs has been restricted or discontinued in Europe but as they leach from the BFR-treated products and are persistent, they are commonly found in nature. Polybrominated diphenyl ethers (PBDEs), hexabromocyclododecanes (HBCDDs), tetrabromobisphenol A and its derivatives (TBBPAs) and other brominated phenols, and polybrominated biphenyls (PBBs) are the main classes. From these PBDEs, HBCDDs and TBBPAs are the most widely used. Their chronic dietary exposure, except a certain PBDE, is not a potential risk for the European consumers at any age (EFSA 2010c, 2011d, 2011e, 2011f, 2012c). BFRs are typically present in fish, meat, milk, egg and their products. The exposure to BFRs can induce adverse effects in liver, in thyroid hormone homeostasis and in reproductive, nervous and immune systems in animals (EFSA 2010c, 2011d, 2011e, 2011f, 2012c; Eriksson et al. 2004; NTP 1993a; OECD 2005; Rice et al. 2007; Van der Ven et al. 2006, 2008; Viberg et al. 2004, 2007). Some of the emerging and novel BFRs might be of importance, particularly related to their genotoxic and carcinogenic properties, but data are missing (EFSA 2012d). PFASs are fluorinated aliphatic man-made chemicals that have been widely used for decades in industrial applications and consumer products. Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS) have been the most extensively applied, but due to their persistence in nature their use has been phased out and replaced by other PFASs (Bull et al. 2014; EFSA 2008g, 2012e, 2018h). At the current levels, the chronic exposures of the average Europeans to PFOA or PFOS cause potential risks for some adult consumers but children are at higher risk (EFSA 2018h). Fish and seafood, as well as meat, eggs, milk and their products and drinking water are the main sources of PFOA and PFOS (EFSA 2018h). Based on the human studies, the increased serum cholesterol level is the critical effect following the exposure to PFOA and PFOS, but its causality with diabetes, obesity and metabolic syndrome has not been sufficiently demonstrated (EFSA 2018h; Eriksen et al. 2013; Nelson et al. 2010; Steenland et al. 2009). PFOA and PFOS are not genotoxic or carcinogenic in humans (EFSA 2018h). Currently, the EFSA risk assessment for other PFASs is on-going.

4.2. Food process contaminants

Process contaminants are chemical substances that form in food when the food ingredients undergo chemical modifications during food processing. Fermentation, smoking, drying and high-temperature cooking are such processes where these changes may occur. Acrylamide, PAHs (see above), 3-MCPD, glycidyl ester, furan and ethyl carbamate are food process contaminants that can co-occur in the foods and diets with the other contaminants.

4.2.1. Acrylamide, furan and methylfurans

Since the mankind began cooking, humans have exposed to acrylamide. It is a highly water-soluble organic substance, also used as an industrial chemical, which forms during thermal food processing. Currently, the chronic dietary exposure to acrylamide, poses a potential health risk for the Europeans at all age (EFSA 2015b). The foods making the largest contributions to the exposure are fried potato products, biscuits, crackers, bread and coffee. Smoking is an important non-dietary source (EFSA 2015b). Acrylamide cannot be eliminated from the cooked starchy foods but frying and toasting light and avoiding storing potatoes in a refrigerator reduce the levels. The metabolite of acrylamide reacts directly with DNA and is mutagenic, and is probably responsible for the cancers observed in the animals exposed to acrylamide. In fact, research has not demonstrated that acrylamide is a human carcinogen and IARC has classified it as 'probably carcinogenic to humans' (group 2A) (EFSA 2015b; NTP 2012). Like to acrylamide, humans are exposed to furans while cooked or heated foods are consumed. Furan, 2-methylfuran, 3-methylfuran and 2,5-dimethylfuran are volatile organic substances that are formed while food is thermally processed (EFSA 2017c). The present dietary exposure to furans is a potential risk for the Europeans at all age, coffee being the major source of exposure for adults (EFSA 2017c). Grains and grain-based foods are less important sources for adults but important for children. As furan is a volatile substance, its levels can be reduced in some foods e.g. by heating and stirring foods in an open saucepan or boiling the coffee instead of preparing it in a coffee machine (EFSA 2017c; JECFA 2011). Furan is toxic to liver and causes liver cancer in animals, and it may be directly DNA-reactive genotoxic carcinogen (EFSA 2017c; Moser et al. 2009; NCTR 2015; NTP 1993b; Von Tungeln et al. 2017). IARC has classified furan as 'possibly carcinogenic to humans' (group 2B) (JECFA 2011; EFSA 2017c).

4.2.2. 3-MCPD, 2-monochloropropane-1,2-diol (2-MCPD), glycidyl esters and ethyl carbamate

3-MCPD and 2-MCPD are chlorinated derivatives of glycerol. They together with the fatty acid esters of 3- and 2-MCPD and glycidol fatty acid esters are unintentionally produced in vegetable oils, mainly palm oil, on refining (EFSA

2016a). Potential risks from the 2-MCPD exposure are not known due to the lack of data but the present chronic dietary exposure to 3-MCPD does not pose a potential risk for the average adult consumers in Europe. Some young children following specific diets might be at risk (EFSA 2016a, 2018i). The chronic dietary exposure to glycidol fatty acid esters causes a low potential risk for the average adult consumers, while the potential risk is higher for the children (EFSA 2016a). The main sources of the exposure are vegetable fats and oils, margarine, bakery products, fired potato products and meat. In the animals, 3-MCPD impacts adversely on renal function and glycidol is a genotoxic carcinogen directly reacting with DNA, classified by IARC as 'probably carcinogenic to humans' (group 2A) (Cho et al. 2008; EFSA 2016a, 2018i; NTP 1990). Ethyl carbamate is an organic substance that is naturally present in fermented foods and alcoholic beverages. Its chronic dietary exposure poses a low potential risk for those average Europeans who do not drink alcohol, while those who drink are at a risk. Ethyl carbamate, by acting through its metabolites, is a genotoxic carcinogen with direct DNA-reactivity in animals. Lung tumors have been observed in animals (EFSA 2007a; JECFA, 2006; NTP 2004). IARC has classified it as 'probably carcinogenic to humans' (group 2A), while alcoholic beverages and ethanol bear the IARC classification 'carcinogenic to humans' (group 1) (EFSA 2007a; IARC 2010b).

4.3. Natural toxins

Natural toxins are produced by living organisms and are therefore naturally present in nature in complex mixtures. They are organic substances with chemical structures from small size molecules to large complicated chemical structures. Mycotoxins are secondary metabolites of fungal species and they form a large class of agricultural contaminants. Plant toxins are secondary metabolites of plants, and thus inherited substances in certain plants. Some plant toxin groups have hundreds of analogs to contaminate crops and plant-based foods. Algal marine biotoxins form many highly heterogeneous families with a high number of different chemical analogs. They are shellfish, fish and seafood contaminants produced by various algal species during harmful algae blooms in the marine environment. The natural toxin levels have a high seasonal and annual variation because their production depends on climatic conditions. Therefore, the dietary exposures and health risks can vary over the time.

4.3.1. Mycotoxins

4.3.1.1. Aflatoxins. Aflatoxins are produced by *Aspergillus* fungi which typically in Europe grow on the crops under the southern climate. Several aflatoxin analogs are known, but aflatoxin B1 is the most toxicologically and agriculturally relevant. Chronic dietary exposure to aflatoxins has been causally associated with human liver cancer and they are amongst the most potent mutagenic and carcinogenic substances known (JECFA 1999; 2017; Yeh et al. 1989). IARC has classified aflatoxin B1 and natural aflatoxin mixtures as 'carcinogenic to humans' (group 1) (IARC 2012). While aflatoxins seem to have only a minor contributing role in liver cancer in Europe, their chronic dietary exposure nonetheless poses a potential risk for the Europeans (EFSA 2007b). Wheat-based foods are the major contributors to the Europeans' exposure (JECFA 2017), although they are frequently detected in the foods imported to Europe (e.g. nuts and dried fruits) (EFSA 2018j). While they cannot be eliminated, the levels can be reduced by thermal food processing and by cleaning and applying selection steps to grains (EFSA 2018j; JECFA 2017). EFSA is currently re-assessing the risks from the aflatoxin exposure.

4.3.1.2. Deoxynivalenol, T-2 and HT-2 toxins, zearalenone and fumonisins. Deoxynivalenol, T-2 toxin, HT-2 toxin, zearalenone, fumonisin and their structural analogs (known as masked, modified and/or conjugated mycotoxins) are produced by *Fusarium* fungi that commonly grow on grains in the European climate. Even though deoxynivalenol is the most prevalent *Fusarium* toxin, presently the chronic dietary exposure to deoxynivalenol and its analogs does not pose health risk for the average adult consumers, while the average young consumers are at potential risk in Europe (EFSA 2017d). The situation is the same with the exposures to T-2 and HT-2 toxins, to zearalenone and to fumonisins (EFSA 2011g, 2011h, 2014d, 2014e, 2017e, 2017f; JECFA 2017). Cereal-based products are the most important dietary sources for the Europeans (EFSA 2011g, 2011h, 2014d, 2014e, 2017d, 2017e, 2017f; JECFA 2017). The major contributors to the exposure of fumonisins are maize-based foods but in those European countries where maize is not typically eaten, wheat-based foods are the main source (JECFA 2017). The *Fusarium* toxins are generally stable during thermal food processing with only a minor impact on their amounts, while cleaning and selection of harvested cereal grains mitigate their levels (EFSA 2011g, 2011h, 2014d, 2014e, 2017d, 2017e, 2017f; JECFA 2017). The critical chronic effect from the deoxynivalenol exposure is reduced body weight gain observed in animals which is observed at the lower levels of exposure than immunological impairment (EFSA 2017d). The dietary exposure to T-2 and HT-2 toxins was observed to induce immune- and haematotoxicity in animals (EFSA 2011g, 2017e). Zearalenone and its analogs are endocrine disruptors, some analogs with higher potency than zearalenone, and cause estrogenic effects in animals (EFSA 2011h, 2016b, 2017g). The available EFSA risk assessment covers zearalenone alone, but because the amounts of the zearalenone-analogs in the cereal-based foods vary from a few percent to 100% of that of zearalenone (EFSA 2016b), an increased potential risk due to their co-exposure can be assumed. The chronic exposure to fumonisins adversely affect kidney and liver in animals (EFSA 2018d, 2018k; JECFA 2012, 2017). IARC has classified fumonisin B1 as 'possibly carcinogenic to humans' (group 2B) but fumonisins and their analogs do not react directly with DNA (JECFA

2017). The dietary exposure to fumonisins has been claimed to exert cancers in humans but a causal link has not been confirmed (EFSA 2018d; JECFA 2017).

4.3.1.3. Ochratoxin A. Ochratoxin A is produced by *Penicillium* and *Aspergillus* fungal species. The current chronic dietary exposure to ochratoxin A is not a potential risk for the average adult European consumers (EFSA 2006a; JECFA 2008), cereal-based foods, wine, fruit juice and coffee being the main sources of exposure (EFSA 2006a; JECFA 2001, 2008). Its exposure exerts adverse effects in kidney in animals and IARC has classified ochratoxin A as 'possibly carcinogenic to humans' (group 2B) but it appears not to be directly genotoxic. Causality of human nephropathy with the dietary exposure to ochratoxin A has been suggested but not established (EFSA 2006a, 2010d; JECFA 2008). EFSA is currently re-assessing the risks from the ochratoxin A dietary exposure.

4.3.1.4. Ergot alkaloids, Alternaria toxins, nivalenol, diacetoxyscirpenol, moniliformin, beauvericin and enniatins. Many less prevalent mycotoxins with generally low concentrations in foods can add to the Europeans' total mycotoxin exposure, but paucity in the available data has made their risk assessments uncertain. The chronic dietary exposures to *Alternaria* toxins (tenuazonic acid and tentoxin), to 12 different ergot alkaloids and to nivalenol do not pose potential risks for the average European consumers at any age, while a low health concern arises from the exposure to moniliformin (EFSA 2011b, 2012f, 2013c, 2016c, 2017h, 2018l). The chronic exposure to diacetoxyscripneol is not a risk for the average consumers at any age in Europe (EFSA 2018m). For the many *Alternaria* toxins, including genotoxic alternariol and alternariol monomethyl ether, as well as for citrinin and sterigmatocystin, the lack of data has prevented the risk assessment (EFSA 2011b; 2012g, 2013d; JECFA 2017). Sterigmatocystin shares its biosynthetic pathway with aflatoxins and is a mutagenic carcinogen, and also citrinin may have genotoxic carcinogenic properties (EFSA 2012g, 2013d; JECFA 2017). However, their occurrence in the European foods are low (López et al. 2017; Mol et al. 2015), suggesting low dietary exposures. The equivocal data on toxicity of beauvericin and enniatins led to an uncertain assessment, but their exposures suggest a potential health risk for the average European consumers (EFSA 2014f; Maranghi et al. 2018). Many of these mycotoxins are regarded as emerging toxins because the sensitive analytical methods have lately revealed new data. Cereal-based foods make the greatest contributions to the exposures of these mycotoxins (EFSA 2011b, 2012f, 2011g, 2013c, 2013d, 2016c, 2017h, 2018l, 2018m).

4.3.2. Plant toxins and natural plant constituents

4.3.2.1. Pyrrolizidine alkaloids and tropane alkaloids. Thousands of plants may contain pyrrolizidine alkaloids, and although around 600 of them are currently known, only about 30 are of importance (EFSA 2011i, 2017i). Chronic dietary exposure to these alkaloids poses a potential risk for average European consumers at all age, specifically for frequent and high consumers of teas or herbal infusions and honey (EFSA 2017i). High dietary exposure to pyrrolizidine alkaloids is known to induce acute hepatic human intoxications, including deaths, but for the European consumers the potential risk is low (EFSA 2017i). The most important and most studied 1,2-unsaturated pyrrolizidine alkaloids induce liver cancer in animals by reacting directly with DNA (EFSA 2011i, 2017i; NTP 2003). Some pyrrolizidine alkaloids IARC has classified as 'possibly carcinogenic to humans' (group 2B) (EFSA 2011i, 2017i). Only a couple of over 200 tropane alkaloids have been studied, although some food crops (e.g. potatoes) produce them and others can become contaminated with them during harvesting (EFSA 2013a; Mulder et al. 2016). Dietary exposure to these alkaloids can only acutely affect humans causing neurological effects. Currently, due to the poor occurrence data, only the dietary exposure for toddlers has been assessed indicating a potential risk (EFSA 2013a). However, based on the recent European-wide survey many tropane alkaloids are present in a range of foods, some with high levels (Mulder et al. 2016). This suggests that also other consumers may be at a potential risk.

4.3.2.2. Erucic acid, opium alkaloids and cyanogenic glycosides. The chronic dietary exposure to erucic acid, present at high levels in rape and mustard seeds, is currently not a potential risk for the average European consumers at any age (EFSA 2016d). Similarly, there is no risk from the dietary exposure to opium alkaloids in food-grade poppy seeds (EFSA 2011j, 2018n). Chewing and grinding of raw apricot kernels release cyanide from cyanogenic glycosides and only one small kernel in young children can cause effects, while adults can consume either three small kernels or less than half of a large one (EFSA 2016e). The exposure to cyanide induces high acute toxicity in humans and can cause a death. EFSA is currently assessing potential risks from the exposure to several other natural plants toxins (EFSA 2018o).

4.3.2.3. Nitrate. Nitrate is a naturally occurring substance with substantial amounts in leafy crops and vegetables, and an approved food additive. The type of vegetable and growing conditions largely affect the nitrate levels (EFSA 2008a). Fruits are low in nitrate. Considering all exposure sources of dietary nitrate (natural presence (e.g. vegetables), food additive and contamination), the average European consumers do not have health concerns but children may be at the potential risk (EFSA 2008a, 2010e, 2017j). Vegetables and vegetable-based foods make the greatest contributions to the exposure; 5% is from food additives (EFSA 2017j). Thermal food processing, washing and peeling mostly reduce the nitrate levels (EFSA 2008a; Ekart et al. 2013). The intrinsic toxicity of nitrate is relatively low, but the exposure to its metabolites and reaction products (e.g. nitrite, nitric oxide and N-nitroso compounds) may adversely impact health due to carcinogenicity and methaemoglobinaemia (EFSA 2008a).

In the human mouth, saliva converts nitrate to nitrite which may endogenously form N-nitroso compounds, of which many are carcinogenic. Their produced levels, however, represent of low health concern (EFSA 2017j).

4.3. Marine biotoxins

Marine biotoxins, which after harmful algal blooms can be present in shellfish, certain fish and seafood, comprise several toxin-groups. The most common ones in the European seas are okadaic acid-, azaspiracid-, saxitoxin-, yessotoxin- and pectenotoxin-group of toxins and domoic acid (EFSA 2008b, 2008c, 2008h, 2009e, 2009f, 2009g). For the average seafood consumers, the chronic health risks are currently unknown due to the missing data, but some European consumers eating regularly high amounts of shellfish could be at potential risk, in particular because the EU MLs are not protective enough (EFSA 2010f; 2009h). These toxins are highly toxic whose dietary exposure exerts acute effects in humans with a wide range of symptoms from slight tingling sensation or numbness around the lips to death. Several other marine biotoxins (ciguatoxin-, tetrodotoxin-, brevetoxin- and palytoxin-group of toxins and cyclic imines) do not have EU MLs, but are less prevalent in the European waters (EFSA 2009g, 2009h, 2009i, 2010a, 2010g, 2010h, 2017a). Thermal food processing can either increase or lower the toxin levels in shellfish (EFSA 2009j). Cyanobacteria (blue-green algae) in the surface waters and marine environments can produce cyanotoxins, which may contaminate drinking water and food, but the Europeans' exposure levels are currently unknown (Testai et al. 2016).

4.4. Other chemical contaminants

4.4.1. Mineral oil hydrocarbons, melamine, organotin and chlorate

Mineral oil hydrocarbons form highly complex mixtures which are divided to two main types, mineral oil saturated and mineral oil aromatic hydrocarbons, not possible to separate to individual compounds. Their presence in foods can originate from variable sources, such as food contact materials, printing inks, wax food coatings, food additives and pesticides (EFSA 2012h). Prevention strategies, e.g. use of functional barriers in food packaging materials, are applied to mitigate their migration. They may also enter to food e.g. from different oils, debris from tyres and road bitumen (EFSA 2012h). At present, the dietary exposures to both types of mineral oil mixtures pose a potential risk for the Europeans and a variety of foods contribute to the exposure. The exposure to mineral oil aromatic hydrocarbons rises concerns because they are possibly carcinogens reacting directly with DNA, and the exposure to mineral oil saturated hydrocarbons, specifically when white oils are used as non-stick agents in baking (Baldwin et al. 1992; EFSA 2012h; Ingram et al. 2000; Mackerer et al. 2003; Smith et al. 1996). The background exposure to the aromatic fraction appears to be 15-35% of the total mineral oil hydrocarbons (EFSA 2012h). In animal studies, the mineral oil saturated hydrocarbons accumulate in tissues and cause liver inflammations (EFSA 2012h). Melamine is an organic chemical used as food contact materials. It can also form from specific pesticides, veterinary medicines or disinfectants. Currently dietary melamine does not pose a potential risk for the Europeans (EFSA 2010i). The situation is the same with the dietary exposure to organotins, widely used as pesticides, polyvinyl chloride stabilizers, biocides and certain paints (EFSA 2004). Chlorate is an inorganic substance which presence in the diet originate from the legal use of chlorine disinfectants in drinking water treatment and disinfection of food preparation surfaces (EFSA 2015e). For the average European adult consumers, the current dietary exposure to chlorate is not a risk but poses a potential risk for the children (EFSA 2015e). The main source of the dietary exposure is drinking water but also frozen foods contribute. Chlorate can inhibit iodine uptake in animals (EFSA 2015e).

4.4.2. Contaminants and plastic additives in microplastics and nanoplastics

Plastics and plastic debris are widely known to contaminate seas and lakes. While microplastics are either from fragmented plastic material or were engineered to be that size, the nanoplastics are either from manufactured materials or from fragmented microplastics. Only microplastics smaller than 150 µm may cause exposure. Nanoplastics are assumed to cause an exposure but data are currently missing. Microplastics can contain on average 4% of various organic and inorganic plastic additives and they can adsorb chemical contaminants. POPs, PAHs, PCBs, phthalates, bisphenol A and PBDEs have been detected in microplastcis. The present dietary exposure to the contaminants and additives from seafood contaminated with microplastics has only a minor addition to the total exposure, but little is known about these materials (EFSA 2016f).

5. Intentionally used chemicals in foods and their residues

5.1. Food improvement agents (food additives, enzymes and flavorings)

Food additives are added to food to perform specific technological functions in manufacture, processing, preparation, treatment, packaging, transport or storage, and therefore they become a part of the food. These substances are not normally consumed as foods or used as food ingredients. They are used for a variety of purposes, like for food preservation to prolong shelf-life, such as commonly used lactic acid to preserve food from microbial spoilage, or antioxidants to protect the food against oxidation (e.g. ascorbic acid (vitamin C), tocopherols (vitamin E)). Processing aids, such as flour treatment agents, are added to flour or dough to improve the baking quality. Food colors are commonly used to add color to foods that are colorless, colored differently or restore the loss of the color. Food flavorings, which give or change the odor or taste, have a long history of safe use (EFSA 2018p). Sweeteners impart a sweet taste of the food or are used as table-top sweeteners such as aspartame, an intense low-calorie artificial sweetener. Natural food enzymes have been used in the food production for centuries and are therefore considered safe. Antioxidants, colors, emulsifiers, stabilizers, gelling agents, thickeners, preservatives and sweeteners are the most commonly used food additives in the industrial food production (EFSA 2018q). The levels of food improvement agents present in foods are monitored by the national food safety authorities in Europe.

5.2. Food contact materials

Food is in contact with many materials and articles during its production, processing, storage, preparation and serving, before it is consumed (EC 2018e). Common materials and articles are packaging and containers, kitchen equipment, cutlery, dishes, bottles, food processing equipment and production machinery. They are made of a large range of materials, such as plastics, ceramics, rubber, paper, metal, and their combinations (EC 2018e). Nowadays, the active and intelligent packing materials are also used. The food contact materials have to be sufficiently inert not to release their constituents into food at the residue levels negatively influencing human health or food quality. Therefore, the chemicals can migrate into the food within their specified migration residue levels, like certain heavy metals from the ceramics or bisphenol A from the plastic materials (EC 2018e). Bisphenol A has been under controversy but at the current levels of exposure there is no potential risk and the health concern is low from combined exposure (diet, dust, cosmetics and thermal paper) (EFSA 2015f). However, some European countries have banned its use in plastic food contact materials and recently the European Chemicals Agency identified bisphenol A as "substance of very high concern" (ECHA 2018). Currently, bisphenol A is prohibited to use in food packing for children in the EU (EC 2018f) and EFSA is reevaluating it.

5.3. Pesticides

Plant protection products (pesticides, fungicides, insecticides and growth regulators), commonly known as pesticides, are agrochemicals which prevent, destroy, or control a harmful organism (pests and weeds) or disease, or they protect plants and plant products during production, storage and transport. In the past 20 years, the Europeans' dietary exposure has been low because constantly 97% of the foods tested for pesticides have been compliant with the legal levels. More than 80,000 food samples for over 700 different pesticides (about 220 per a sample) are analyzed annually (EC 2018g; EFSA 2017k, 2018r). Infants and young children, however, may have a potential risk at the current exposure levels for some pesticides (EFSA 2018s). Chemical pesticides contain one or more active substances that form the activity of the pesticide product. Currently, about 400 active substances have an EU-authorization, which is 50% fewer than 25 years ago (EC 2018g, 2018h; EFSA 2017k; 2018r). Nowadays, adverse effects via endocrine disruption at low-doses need also to be determined for pesticides (ECHA and EFSA 2018).

5.4. Veterinary medicinal products

Veterinary medicinal products are used to treat food producing animals to prevent or cure disease. The dietary exposure of the Europeans to veterinary medicinal residues is nearly negligible due to the high regulatory compliance. Only 0.25-0.37% of the targeted samples have been non-compliant with the regulatory limits in the past nine years (EFSA 2018t). Some European countries, however, have more non-compliant results than others (EFSA 2018t; EC 2018i). In 2016, nearly 720,000 samples were analyzed consisting of about 370,000 targeted samples and over 21,000 suspect samples in addition to samples from import and national programs. The use of hormonal growth promotors was prohibited in Europe in 1981 (EC 2018i).

6. Health benefits of the foods over the potential risks from the chemicals

Carbohydrates, fats, proteins, vitamins, minerals and water are important nutrients. They are beneficial to humans when their dietary exposures are at the appropriate levels required by the biological functions of the human body (EFSA 2019d). The dietary reference values have been established on the amount of nutrients needed to maintain health in healthy people (EFSA 2019d). The dietary reference values also advice the maximum nutrient amount to which humans can safely expose to for a long term. However, those individuals who suffer from illness may have different nutritional needs from the dietary reference values (EFSA 2019d). Consumption of substantial amounts of vegetables and fruits is considered beneficial and they are important part of balanced healthy diet. Currently, a consumption of 400 g/day of vegetables and fruits is recommended by WHO. Vegetables, fruits and their products provide many biologically active substances and nutrients, such as vitamins, minerals, flavonoids, carotenoids, fiber and protein (EFSA 2008a; IARC 2003). Lack of saturated fat and low sodium levels further contribute to their beneficial nutritional properties, although the benefits cannot be linked to a single or mixture of substances (EFSA 2008a; WHO 2003). High fiber consumption has been associated with its beneficial effects to protect against development of non-communicable diseases (Reynolds et al. 2019). Vegetables and fruits are essential in the weight management and can lower the risk for non-communicable diseases (EFSA 2008a; IARC 2003, 2004; WHO 2002; Willett et al. 2019). Consumption of certain vegetables and fruits may, however, cause negative health effects arising from exposure to antinutrients or allergens (EFSA 2008a; IARC 2003, 2004). Cereals are the core of human nutrition (FAO 2015; Willett et al. 2019) and an essential part of the daily diet. They are important energy sources and contain a wide range of nutrients. Cereals are low in fat and contain unsaturated fatty acids which are beneficial in weight management. Their fiber is important for maintaining the digestive system. High dietary fiber can also protect against development of non-communicable diseases (Reynolds et al. 2019). Cereal consumption has been associated with several specific health benefits (Björck et al. 2012). Cereals, however, also consist of allergens and gluten is known to cause celiac disease.

Animal-based foods are important diet components and sources of energy, protein, vitamins and minerals. Fish and seafood consumption has been recognized to be beneficial to humans and therefore recommendations for consumption are made by many EU MSs (EFSA 2014c). Fish and seafood contain micronutrients such as vitamin D which is required for efficient calcium absorption and for normal bone mineralization (EFSA 2008i). Fish is also high in essential n-3 long-chain polyunsaturated fatty acids which has recognized beneficial effects to reduce cardiovascular disease risk factors (EFSA 2014c, 2015a; Willett et al. 2019). About 1-2 servings of fish and seafood per week have been associated with a lower risk of coronary heart disease mortality in adults (EFSA 2014c). These fatty acids in fish may counteract with the negative neurodevelopmental outcomes associated in humans due to the methylmercury exposure (EFSA 2012a, 2014c; Willett et al. 2019). Fish and seafood may, however, also trigger allergies. Red meat is the only natural source for vitamin B12 and a rich source for other B vitamins and minerals. The human bioavailability of minerals is higher in red meat than in plant-based foods (IARC 2018). Recently, IARC allocated the consumption of red meat (i.e. raw and cooked) to group 2A 'probably carcinogenic to humans' and consumption of processed meat to group 1 'carcinogenic to humans' (IARC 2014, 2018). As multiple chemicals in meat, which many are formed during cooking or processing, may potentially induce cancer (e.g. heme iron, N-nitroso compounds, heterocyclic aromatic amines, lipid peroxidation products and PAHs), the carcinogenicity cannot be linked to a particular substance in meat (IARC 2018). The possible health risks (and benefits) from the red meat consumption are yet to be assessed comprehensively by the international risk assessment bodies. However, recently Willett et al. (2019) evaluated that it is plausible the risks of cardiovascular and other non-communicable diseases associated with the high red meat consumption, processed red meat particularly, are due to multiple constituents in meat (e.g. fat (saturated fat), heat-induced carcinogens and heme iron). Similar association was not observed for white meat (poultry and fish). Willett et al. (2019) concluded that it is beneficial to eat less red meat and proposed portion sizes for red and white meat consumption in a daily healthy diet.

7. Climate change may alter the dietary exposure to certain contaminants

Climate change may pose emerging risks defined as 'risks resulting from a newly identified hazard to which a significant exposure may occur or from an unexpected new or increased significant exposure and/or susceptibility to a known hazard' (EFSA 2007c). During the changing climate, air and sea water temperatures and variability in rainfalls increase, and the salinity and nutrients in sea waters change. These factors are expected to shift the geographic distributions and incidence of the natural toxin-producing living organisms in Europe (Battilani et al. 2012, 2013, 2016; Janić Hajnal et al. 2017; Marvin 2012; Naustvoll et al. 2012; Parikka et al. 2012; Van der Fels-Klerx et al. 2012a, 2012b). Generally, higher incidence and levels of mycotoxins are expected to occur but also lower occurrence may take place (Battilani et al. 2012, 2013; Van der Fels-Klerx et al. 2012a, 2012b, 2016). The aflatoxin prevalence and levels are anticipated to increase in Europe, while their occurrence from the south expands to the central Europe (Battilani et al. 2012, 2013, 2016). In the recent past, the highly aflatoxin-contaminated maize in the Balkan-area led to compromise the food safety over the food security, by permitting an exceedance of the legal limits (Janić Hajnal et al. 2017; Kos et al. 2013; Krska et al. 2016). In 2013, the high levels of *Fusarium* toxins in maize in the central Europe led to a request for a temporary increase of the EU MLs (EFSA 2014e). The elevated mycotoxin levels imply that the food material is wasted due to the regulatory noncompliance. Therefore, in order to manage the risks proportionately and secure the food supply, it has been assessed whether an increase of the EU MLs could cause an unacceptable increase in the health risks (EFSA 2006, 2009k, 2013e, 2014e, 2018j).

Warmer water environments, may increase the harmful algal blooms, shift the blooms to previously bloom-free waters, and permit new invasive toxic algal and fish species to enter to the European waters. This can lead to the elevated toxin levels and novel toxins in the European fish and seafood. In 2003, ciguatoxins producing algae were reported for the first time in Europe (EFSA 2010a). First human intoxications from the dietary exposure to them and to other emerged marine biotoxins, tetrodotoxins, were reported few years later (EFSA 2010a, 2017a). Since then, tetrodotoxins in seafood grown in Europe have been detected (EFSA 2017a). Changing climate may also reduce the harmful algal blooms and marine biotoxin levels, as reported in the northern Europe (Naustvoll et al. 2012). An increase in the dietary exposure to heavy metals and organic pollutants may also occur, because the forest fires can generate variety of organic pollutants and mobilize the heavy metals in soils. Floods can transport contaminants to uncontaminated locations (Abraham and Dowling 2017; Thomson and Rose 2011). Warmer waters decrease salinity and facilitate methylation of mercury increasing the intake of methylmercury and other heavy metals by fish and shellfish. The elevated temperatures can also increase the bioavailability of the pollutants deposited in the sediments (Niinemets et al. 2017; Thomson and Rose 2011).

8. Dietary contaminants of health concern and their risk ranking

Based on about the 100 European-level contaminant risk assessments, the chronic dietary exposures to those chemical contaminants, which appear to be hard to manage, pose

Table 1. Chemical contaminants that pose potential health risks for the average adult European consumers from the chronic dietary exposure and their critical adverse health effects.

Chemical contaminant	Critical adverse health effect	Reference
Lead	Chronic kidney disease	EFSA 2010b
Cadmium	Kidney dysfunction	EFSA 2009d
Arsenic	Lung, urinary bladder and skin cancer, skin lesions	EFSA 2009c, 2014b
Nickel	Reproductive and developmental effects	EFSA 2015c
Dioxins and dl-PCBs	Impaired sperm quality	EFSA 2018g
PBDE (BDE-99)	Neurodevelopment	EFSA 2011a
PFOS, PFOA	Increased serum cholesterol	EFSA 2018h
Acrylamide	Carcinogenic effects	EFSA 2015a
Furan and methylfurans	Liver damage, liver cancer	EFSA 2017c
Ethyl carbamate	Lung cancer	EFSA 2007a
Aflatoxins	Human liver cancer	EFSA 2007b, JECFA 2017
Pyrrolizidine alkaloids	Liver cancer	EFSA 2011i, 2017i
Mineral oil hydrocarbons	Carcinogenic effects, liver microgranulomas	EFSA 2012h

potential risks for the average European adult consumers. These are persistent environmental pollutants: dioxins and dl-PCBs, PFOS, PFOA and a BFR, process contaminants: acrylamide, furans and ethyl carbamate (for alcohol drinkers) and heavy metals and nickel. Remarkable is that the contaminants posing low potential chronic risks are also process contaminants (glycidol esters, PAHs and ethyl carbamate (alcohol non-drinkers)), environmental contaminants (PAHs) and a metal (chromium). From the large number of natural toxins, it is only a dietary exposure to aflatoxins and pyrrolizidine alkaloids that poses potential chronic risks. The current potential health risks arise also from the chronic exposure to mineral hydrocarbon mixtures in food. These contaminants together with their critical adverse effects are presented in Table 1. Notable is that the potential risks identified at the European level by EFSA appear to concur well with the outcomes of the national TDSs of France (ANSES 2011, 2016), even if the European level risk assessments may overlook the national specificities (e.g. dietary habits).

An attempt was made to rank the chronic risks of the identified contaminants (Table 1) by considering the type of critical effect they induce and whether the exposure is regular from foods consumed daily. Consequently, this ranking is very simple and limited to those contaminants identified by EFSA to pose chronic risks in adults. It does not take into account the uncertainties of the EFSA risk assessments (such as lack of toxicity or occurrence data). Thus, this risk ranking should be regarded as indicative only. When ranking the chronic potential risks of the contaminants (Table 1), the food process contaminants rank the first followed by mineral oil hydrocarbons (aromatic fraction). This because of their genotoxicity and carcinogenicity, although not verified in humans, and a wide prevalence in many daily consumed foods. Aflatoxins rank the next due to their exposures from highly consumed wheat-based foods and a high genotoxic-carcinogenic potency inducing human liver cancer. Dioxins and dl-PCBs, nickel and a BFR can be ranked then owing to their exposures from the foods commonly eaten every day, followed by pyrrolizidine alkaloids, even if genotoxic-carcinogens, due to their specific sources of dietary exposure. The least alarming ones are PFOS, PFOA and the heavy metals, although present in many foods, as their exposures pose potential risks only to some European adults. As the chronic exposures of these contaminants are from the foods consumed on daily basis, it is their mixture to which the average European adult consumer exposes every day. It is very noteworthy that several of these contaminants are genotoxic-carcinogens (i.e. have a similar mode of action) and potentially induce liver cancer or adversely affect liver. Therefore, the combined risk from the exposure to the mixture can be expected to be greater than the present risks assessed for single chemicals based on the dose-addition principle as proposed by EFSA for the mixture risk assessment (EFSA 2018e, 2018f, 2019b, 2019c).

9. Conclusion

Although the Europeans expose to large mixtures of beneficial and harmful dietary chemicals every day, only potential risks from the mixtures of those chemical analogs with a similar mode of action (e.g. dioxins, PAHs and natural toxins) have been assessed. Health benefits from the beneficial dietary chemicals in conjunction with the potential risks from the hazardous chemicals are hardly considered. Only two EFSA-assessments, nitrate in vegetables and methylmercury in fish, considered both risks and benefits. It is of an alarming concern that on each day the average European adult food consumers currently exposure to a mixture of potentially genotoxic-carcinogenic contaminants, particularly food process contaminants, at the potential risk levels. The chronic dietary exposures to other dietary chemical contaminants also pose potential health risks. However, as they lack genotoxic-carcinogenic properties, the potential risks from the exposures to these contaminants appear to be lower and can be managed by decreasing the exposures below the HBGVs. Red meat consumption has received much attention recently due to its carcinogenicity in humans and other negative health outcomes. However, the read meat consumption lacks currently a comprehensive risk (and benefit) assessment but mixtures of chemicals and food constituents are the cause for its carcinogenicity and for the other non-communicable diseases it can induce. It has to be borne in mind that a human body has many biological and biochemical mechanisms to overcome the adverse effects. The effects from beneficial food chemicals together with the biological functions of the human body, interact with the toxic effects. To keep the dietary exposures to chemical contaminants at the appropriately low levels, a balanced diet with an array of different foods with varying quantities and avoiding high consumption of any specific foods, is vital. Major novel developments are required before risk-benefit mixture assessments (or at a next step dietary-exposome assessment) at the EU-level can be conducted, in particular mixture toxicity data are needed. Over the time the Europeans' dietary exposures to the chemical contaminants of health concern are expected to decline, when the new EU risk management actions show their efficacy.

Acknowledgments

This review would not have been possible without the contributions of the scientists whose work formed the basis of the risk assessments done by EFSA and the work done by EFSA staff over the past 15 years.

Declaration of interest

The authors declare they have no competing financial interests.

Funding

This work was supported by the European Union Horizon 2020 research and innovation program under grant agreement No 692195 ('MultiCoop').

References

Abraham, J., and K. Dowling. 2017. The unquantified risk of post-fire metal concentration in soil: A review. *Water Air and Soil Pollution* 228 (175):1–33.

Ahsan, H., Y. Chen, F. Parvez, L. Zablotska, M. Argos, I. Hussain, H. Momotaj, D. Levy, Z. Q. Cheng, V. Slavkovich., et al. 2006. Arsenic exposure from drinking water and risk of premalignant skin lesions in Bangladesh: Baseline results from the health effects of arsenic longitudinal study. *American Journal of Epidemiology* 163 (12):1138–48. doi: 10.1093/aje/kwj154.

Åkesson, A., P. Bjellerup, T. Lundh, J. Lidfeldt, C. Nerbrand, G. Samsioe, S. Skerfving, and M. Vahter. 2006. Cadmium-induced effects on bone in a population-based study of women. *Environmental Health Perspectives* 114 (6):830–4. doi: 10.1289/ehp.8763.

Alfvén, T., C. G. Elinder, M. D. Carlsson, A. Grubb, L. Hellström, B. Persson, C. Pettersson, G. Spang, A. Schütz, and L. Järup. 2000. Low-level cadmium exposure and osteoporosis. *Journal of Bone and Mineral Research* 15 (8):1579–86. doi: 10.1359/jbmr.2000.15.8.1579.

Alfvén, T., C. G. Elinder, L. Hellström, F. Lagarde, and L. Järup. 2004. Cadmium exposure and distal forearm fractures. *Journal of Bone and Mineral Research* 19 (6):900–5. doi: 10.1359/JBMR.040202.

Amzal, B., E. Christoph, and J. L. Dorne. 2009. Meta-analysis of dose-effect relationship of cadmium for benchmark dose evaluation. Assessment Methodology Unit, Technical report of EFSA. *EFSA Journal* 254:62.

ANSES. 2011. Second French Total Diet Study (TDS 2) Report 1. Inorganic contaminants, minerals, persistent organic pollutants, mycotoxins and phytoestrogens. French Agency for Food, Environmental and Occupational Health & Safety. ANSES Opinion, 301.

ANSES. 2016. Total Diet Studies (TDSs): A realistic approach for determining nutritional and health risks related to food. Updated 21.9.2016. Accessed 18 July 2018. https://www.anses.fr/en/content/total-diet-studies-tdss.

Baldwin, M. K., P. H. Berry, D. J. Esdaile, S. L. Linnett, J. G. Martin, G. C. Peristianis, R. A. Priston, B. J. Simpson, and J. D. Smith. 1992. Feeding studies in rats with mineral hydrocarbon food grade white oils. *Toxicologic Pathology* 20 (3-1):426–35. doi: 10.1177/019262339202000312.

Battilani, P., M. Camardo Leggieri, V. Rossi, and P. Giorni. 2013. AFLA-maize, a mechanistic model for Aspergillus flavus infection and aflatoxin B1 contamination in maize. *Computer and Electronics in Agriculture* 94:38–46. doi: 10.1016/j.compag.2013.03.005.

Battilani, P., V. Rossi, P. Giorni, A. Pietri, A. Gualla, H. J. van der Fels-Klerx, C. J. H. Booij, A. Moretti, A. Logrieco, F. Miglietta, et al. 2012. Modelling, predicting and mapping the emergence of aflatoxins in cereals in the EU due to climate change. European Food Safety Authority. *EFSA Supporting Publication* 9:EN-223, 172.

Battilani, P., P. Toscano, H. J. Van der Fels-Klerx, A. Moretti, M. Camardo Leggieri, C. Brera, A. Rortais, T. Goumperis, and T. Robinson. 2016. Aflatoxin B1 contamination in maize in Europe increases due to climate change. *Scientific Reports* 6:24328. doi: 10.1038/srep24328.

Benford, D. 2017. Risk assessment of chemical contaminants and residues in food. In *Chemical contaminants and residues in food*, eds. D. Schrenk and A. Cartus, 3–13. Duxford, UK: Woodhead Publishing.

Björck, I., E. Östman, M. Kristensen, N. M. Anson, R. K. Price, G. R. M. M. Haenen, R. Havenaar, K. E. Bach Knudsen, A. Frid, H. Mykkänen, et al. 2012. Cereal grains for nutrition and health benefits: Overview of results from in vitro, animal and human studies in the HEALTHGRAIN project. *Trends in Food Science & Technology* 25:87–100. doi: 10.1016/j.tifs.2011.11.005.

Bull, S., K. Burnett, K. Vassaux, L. Ashdown, T. Brown, and L. Rushton. 2014. Extensive literature search and provision of summaries of studies related to the oral toxicity of perfluoroalkylated substances (PFASs), their precursors and potential replacements in experimental animals and humans. Area 1: Data on toxicokinetics (absorption, distribution, metabolism, excretion) in in vitro studies, experimental animals and humans. Area 2: Data on toxicity in experimental animals. Area 3: Data on observations in humans. *EFSA Supporting Publication* 2014:EN-572, 345.

Chiou, H. Y., S. T. Chiou, Y. H. Hsu, Y. L. Chou, C. H. Tseng, M. L. Wei, and C. J. Chen. 2001. Incidence of transitional cell carcinoma and arsenic in drinking water: A follow-up study of 8,102 residents in an arseniasis-endemic area in northeastern Taiwan. *American Journal of Epidemiology* 153 (5):411–8.

CHM. 2018. Stockholm Convention. Protecting human health and the environment from persistent organic pollutants. Accessed 19 April 2018. http://chm.pops.int/.

Cho, W. S., B. S. Han, K. T. Nam, K. Park, M. Choi, S. H. Kim, J. Jeong, and D. D. Jang. 2008. Carcinogenicity study of 3-monochloropropane-1,2-diol in Sprague-Dawley rats. *Food and Chemical Toxicology* 46 (9):3172–7. doi: 10.1016/j.fct.2008.07.003.

Council. 1993. Council regulation (EEC) no 315/93 of February 1993 laying down community procedures for contaminants in food. *Official Journal of the European Communities* L 37:1–5.

Culp, S. J., D. W. Gaylor, W. G. Sheldon, L. S. Goldstein, and F. A. Beland. 1998. A comparison of the tumours induced by coal tar and benzo[a]pyrene in a 2-year bioassay. *Carcinogenesis* 19 (1):117–24.

EC. 2017d. Commission Recommendation (EU) 2017/84 of 16 January 2017 on the monitoring of mineral oil hydrocarbons in food and in materials and articles intended to come into contact with food. *Official Journal of the European Union* L 12:95–6.

EC. 2006b. Commission Recommendation of 17 August 2006 on the prevention and reduction of *Fusarium* toxins in cereals and cereal products. *Official Journal of the European Union* L 234:35–40.

EC. 2013. Commission Recommendation of 27 March 2013 on the presence of T-2 and HT-2 toxin in cereals and cereal products. *Official Journal of the European Union* L 91:12–5.

EC. 2006a. Commission Regulation (EC) No 1881/2006 of 19 December 2006 setting maximum levels for certain contaminants in foodstuffs and its amendments. *Official Journal of the European Union* L 364:5–24. https://eur-lex.europa.eu/homepage.html.

EC. 2016. Commission Regulation (EU) 2016/239 of 19 February 2016 amending Regulation (EC) No 1881/2006 as regards maximum levels of tropane alkaloids in certain cereal-based foods for infants and young children. *Official Journal of the European Union* L 45: 3–5.

EC. 2018d. Commission Regulation (EU) 2018/290 of 26 February 2018 amending Regulation (EC) No 1881/2006 as regards maximum levels of glycidyl fatty acid esters in vegetable oils and fats, infant formula, follow-on formula and foods for special medical purposes intended for infants and young children. *Official Journal of the European Union* L 55:27.

EC. 2018f. Commission Regulation (EU) 2018/213 of 12 February 2018 on the use of bisphenol a in varnishes and coatings intended to come into contact with food and amending regulation (EU) no 10/2011 as regards the use of that substance in plastic food contact materials. *Official Journal of the European Union* L 41:6.

EC. 2017c. Commission Regulation (EU) 2017/2158 of 20 November 2017 establishing mitigation measures and benchmark levels for the reduction of the presence of acrylamide in food. *Official Journal of the European Union* L 304:24.

EC. 2017b. Directorate-General for Agriculture and Rural Development. Agri-food trade statistical factsheet. European Union – China. Extraction date: 14-09-2017. European Commission. Accessed 20 May 2018. https://ec.europa.eu/agriculture/sites/agriculture/files/trade-analysis/statistics/outside-eu/countries/agrifood-china_en.pdf.

EC. 2017a. European Commission – Antimicrobial Resistance. EU Action on Antimicrobial Resistance. Accessed 3 July 2018. www.ec.europa.eu/health/amr.

EC. 2018e. European Commission – Food contact materials. Accessed 11 May 2018. https://ec.europa.eu/food/safety/chemical_safety/food_contact_materials_en.

EC. 2018g. European Commission – Pesticides explained. Accessed 22. May 2018. http://ec.europa.eu/assets/sante/food/plants/pesticides/lop/index.html

EC. 2018h. European Commission – Pesticides in the European Union authorisation and use. Accessed 22 May 2018. https://ec.europa.eu/food/sites/food/files/plant/docs/pesticides_approval-factsheet.pdf.

EC. 2018i. European Commission – Residues of Veterinary medicinal products. Accessed 25 May 2018. https://ec.europa.eu/food/safety/chemical_safety/vet_med_residues_en.

EC. 2018c. Health and Food Safety Directorate General. E-news. Fight against food fraud: Commission's contribution to Europol/Interpol action against fraudulent canned tuna. European Commission. Accessed 6 June 2018. http://ec.europa.eu/newsroom/sante/newsletter-specific-archive-issue.cfm?archtype=specific&newsletter_service_id=327&newsletter_issue_id=8443&page=1&fullDate=Wed%2025%20Apr%202018&lang=default.

EC. 2018b. Horse meat – What has the EU done so far to address the horse meat scandal? Accessed 24 May 2018. https://ec.europa.eu/food/safety/official_controls/food_fraud/horse_meat/timeline_en

EC. 2007. White paper on a strategy for Europe on nutrition, overweight and obesity related health issues. European Commission. COM (2007) 279 final. Brussels, 30 May 2007.

EC. 2018a. AMR: A major European and Global challenge. European Commission. Accessed 1 July 2018. https://ec.europa.eu/health/amr/sites/amr/files/amr_factsheet_en.pdf.

ECHA. 2018. Substance information – 4,4'-isopropylidenediphenol (bisphenol A). European Chemicals Agency. Accessed 9 September 2018. https://echa.europa.eu/substance-information/-/substanceinfo/100.001.133.

ECHA and EFSA. 2018. Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009 European Chemicals Agency (ECHA) and European Food Safety Authority (EFSA) with support from the Joint Research Centre (JRC). *EFSA Journal* 16 (6):5311, 156.

EFSA. 2007c. Definition and description of "emerging risks" within the EFSA's mandate (adopted by the Scientific Committee on 10 July 2007). Scientific Committee and Advisory Forum unit, European Food Safety Authority, EFSA/SC/415 Final. Accessed 2 July 2018. https://www.efsa.europa.eu/en/topics/topic/emerging-risks.

EFSA. 2014b. Dietary exposure to inorganic arsenic in the European population. European Food Safety Authority. *EFSA Journal* 12 (3): 3597, 68.

EFSA. 2019a. European Food Safety Authority, Acrylamide. Accessed 22 April 2019. https://www.efsa.europa.eu/en/topics/topic/acrylamide.

EFSA. 2019d. European Food Safety Authority, Dietary reference values. Accessed 22 April 2019. https://www.efsa.europa.eu/en/topics/topic/dietary-reference-values.

EFSA. 2018e. Draft guidance on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals. For public consultation. European Food Safety Authority, EFSA Scientific Committee, 81. Accessed 27 June 2018. http://www.efsa.europa.eu/en/press/news/180626.

EFSA. 2018f. Draft statement on genotoxicity assessment of chemical mixtures. For public consultation. European Food Safety Authority, EFSA Scientific Committee, 11. Accessed 27 June 2018. http://www.efsa.europa.eu/en/press/news/180626.

EFSA. 2009k. Effects on public health of an increase of the levels for aflatoxin total from 4 μg/kg to 10 μg/kg for tree nuts other than almonds, hazelnuts and pistachios. European Food Safety Authority. *EFSA Journal* 1168:11.

EFSA. 2008e. EFSA statement on the contamination of sunflower oil with mineral oil exported from Ukraine. European Food Safety Authority. *EFSA Journal* 27 May 2008, 3.

EFSA. 2009b. EFSA statement on the potential risks for public health due to the presence of nicotine in wild mushrooms. European Food Safety Authority. *EFSA Journal* 286:47.

EFSA. 2018q. European Food Safety Authority – Food additives. Accessed 4 May 2018. http://www.efsa.europa.eu/en/topics/topic/food-additives.

EFSA. 2018p. European Food Safety Authority – Flavourings. Accessed 4 May 2018. http://www.efsa.europa.eu/en/topics/topic/flavourings.

EFSA. 2018r. European Food Safety Authority – Pesticides. Accessed 13 May 2018. http://www.efsa.europa.eu/en/science/pesticides.

EFSA. 2018o. European Food Safety Authority – Register of Questions. Accessed 15 June 2018. http://registerofquestions.efsa.europa.eu/roqFrontend/login?1.

EFSA. 2014e. Evaluation of the increase of risk for public health related to a possible temporary derogation from the maximum level of deoxynivalenol, zearalenone and fumonisins for maize and maize products. European Food Safety Authority. *EFSA Journal* 12 (5): 3699.

EFSA. 2017b. Guidance on the risk assessment of substances present in food intended for infants below 16 weeks of age. European Food Safety Authority. *EFSA Journal* 15 (5):4849, 58.

EFSA. 2019c. Guidance on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals. *EFSA Journal* 17 (3):5634, 77.

EFSA. 2018c. Guidance on uncertainty analysis in scientific assessments. European Food Safety Authority. *EFSA Journal* 16 (1):5123, 39.

EFSA. 2013b. Joint Statement of EFSA and EMA on the presence of residues of phenylbutazone in horse meat. European Food Safety Authority. *EFSA Journal* 11 (4):3190, 45.

EFSA. 2005a. Opinion of the scientific committee on a request from EFSA related to a harmonised approach for risk assessment of substances which are both genotoxic and carcinogenic. European Food Safety Authority. *EFSA Journal* 282:31.

EFSA. 2012e. Perfluoroalkylated substances in food: Occurrence and dietary exposure. European Food Safety Authority. *EFSA Journal* 10 (6):2743, 55

EFSA. 2018t. Report for 2016 on the results from the monitoring of veterinary medicinal product residues and other substances in live animals and animal products. European Food Safety Authority. EFSA supporting publication 2018:EN-1358, 75.

EFSA. 2018a. Scientific and technical assistance on trans fatty acids. European Food Safety Authority. *EFSA Supporting Publication* 2018: EN-1433, 16.

EFSA. 2015b. Scientific opinion on acrylamide in food. European Food Safety Authority. *EFSA Journal* 13 (6):4104, 321.
EFSA. 2008i. Scientific opinion on a request from the Association de la Transformation Laitière Française related to the scientific substantiation of a health claim on vitamin D and bone growth. European Food Safety Authority. *EFSA Journal* 827:10.
EFSA. 2012c. Scientific opinion on brominated flame retardants (BFRs) in food: brominated phenols and their derivatives. European Food Safety Authority. *EFSA Journal* 10 (4):2634, 42.
EFSA. 2009d. Scientific opinion on cadmium in food. European Food Safety Authority. *EFSA Journal* 980:139.
EFSA. 2014a. Scientific opinion on dietary reference values for chromium. European Food Safety Authority. *EFSA Journal* 12 (10):3845, 25.
EFSA. 2012d. Scientific opinion on emerging and novel brominated flame retardants (BFRs) in food. European Food Safety Authority. *EFSA Journal* 10 (10):2908, 133.
EFSA. 2012f. Scientific opinion on ergot alkaloids in food and feed. European Food Safety Authority. *EFSA Journal* 10 (7):2798, 158.
EFSA. 2016d. Scientific opinion on erucic acid in feed and food. European Food Safety Authority. *EFSA Journal* 14 (11):4593, 173.
EFSA. 2007a. Scientific opinion on ethyl carbamate and hydrocyanic acid in food and beverages. European Food Safety Authority. *EFSA Journal* 551:44.
EFSA. 2014c. Scientific opinion on health benefits of seafood (fish and shellfish) consumption in relation to health risks associated with exposure to methylmercury. European Food Safety Authority. *EFSA Journal* 12 (7):3761, 80.
EFSA. 2011b. Scientific opinion on hexabromocyclododecanes (HBCDDs) in food. European Food Safety Authority. *EFSA Journal* 9 (7):2296, 118.
EFSA. 2010b. Scientific opinion on lead in food. European Food Safety Authority. *EFSA Journal* 8 (4):1570, 151.
EFSA. 2008c. Scientific opinion on marine biotoxins in shellfish – azaspiracids. European Food Safety Authority. *EFSA Journal* 723:52..
EFSA. 2010g. Scientific opinion on marine biotoxins in shellfish – cyclic imines (spirolides, gymnodimines, pinnatoxins and pteriatoxins). European Food Safety Authority. *EFSA Journal* 8 (6):1628, 39.
EFSA. 2009g. Scientific opinion on marine biotoxins in shellfish – domoic acid. European Food Safety Authority. *EFSA Journal* 1181: 61.
EFSA. 2010h. Scientific opinion on marine biotoxins in shellfish – emerging toxins: brevetoxin group. European Food Safety Authority. *EFSA Journal* 8 (7):1677, 29.
EFSA. 2010a. Scientific opinion on marine biotoxins in shellfish – emerging toxins: ciguatoxin group. European Food Safety Authority. *EFSA Journal* 8 (6):1627, 38.
EFSA. 2008b. Scientific opinion on marine biotoxins in shellfish – okadaic acid and analogues. European Food Safety Authority. *EFSA Journal* 589:62.
EFSA. 2009i. Scientific opinion on marine biotoxins in shellfish – palytoxin group. European Food Safety Authority. *EFSA Journal* 7 (12): 1393, 38.
EFSA. 2009f. Scientific opinion on marine biotoxins in shellfish – pectenotoxin group. European Food Safety Authority. *EFSA Journal* 1109:47.
EFSA. 2009e. Scientific opinion on marine biotoxins in shellfish – saxitoxin group. European Food Safety Authority. *EFSA Journal* 1019: 76.
EFSA. 2009h. Scientific opinion on marine biotoxins in shellfish – summary on regulated marine biotoxins. European Food Safety Authority. *EFSA Journal* 1306:23.
EFSA. 2008h. Scientific opinion on marine biotoxins in shellfish – yessotoxin group. European Food Safety Authority. *EFSA Journal* 907: 62.
EFSA. 2010i. Scientific opinion on melamine in food and feed. European Food Safety Authority. *EFSA Journal* 8 (4):1573, 145.
EFSA. 2012h. Scientific opinion on mineral oil hydrocarbons in food. European Food Safety Authority. *EFSA Journal* 10 (6):2704, 185.
EFSA. 2008a. Scientific opinion on nitrate in vegetables. European Food Safety Authority. *EFSA Journal* 689:79.
EFSA. 2008g. Scientific opinion on perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA) and their salts. European Food Safety Authority. *EFSA Journal* 653:131.
EFSA. 2018s. Scientific opinion on pesticides in foods for infants and young children. European Food Safety Authority. *EFSA Journal* 16 (6):5286, 75.
EFSA. 2011a. Scientific opinion on polybrominated diphenyl ethers (PBDEs) in food. European Food Safety Authority. *EFSA Journal* 9 (5):2156, 274.
EFSA. 2010c. Scientific opinion on polybrominated biphenyls (PBBs) in food. European Food Safety Authority. *EFSA Journal* 8 (10):1789, 151.
EFSA. 2008f. Scientific opinion on polycyclic aromatic hydrocarbons in food. European Food Safety Authority. *EFSA Journal* 724:114.
EFSA. 2010e. Scientific opinion on possible health risks for infants and young children from the presence of nitrates in leafy vegetables. European Food Safety Authority. *EFSA Journal* 8 (12):1935, 42.
EFSA. 2011i. Scientific opinion on pyrrolizidine alkaloids in food and feed. European Food Safety Authority. *EFSA Journal* 9 (11):2406, 134.
EFSA. 2011c. Scientific opinion on tetrabromobisphenol A (TBBPA) and its derivatives in food. European Food Safety Authority. *EFSA Journal* 9 (12):2477, 67.
EFSA 2011d. Scientific opinion on hexabromocyclododecanes (HBCDDs) in food. *EFSA Journal* 9 (7):2296.
EFSA 2011e. Scientific opinion on polybrominated diphenyl ethers (PBDEs) in food. *EFSA Journal* 9 (5):2156
EFSA 2011f. Scientific opinion on tetrabromobisphenol A (TBBPA) and its derivatives in food. *EFSA Journal* 9 (12):2477.
EFSA. 2013a. Scientific opinion on tropane alkaloids in food and feed. European Food Safety Authority. *EFSA Journal* 11 (10):3386, 113.
EFSA. 2016e. Scientific opinion on the acute health risks related to the presence of cyanogenic glycosides in raw apricot kernels and products derived from raw apricot kernels. European Food Safety Authority. *EFSA Journal* 14 (4):4424, 47.
EFSA. 2018d. Scientific opinion on the appropriateness to set a group health-based guidance value for fumonisins and their modified forms. European Food Safety Authority. *EFSA Journal* 16 (2):5172, 75.
EFSA. 2017e. Scientific opinion on the appropriateness to set a group health-based guidance value for T2 and HT2 toxin and its modified forms. European Food Safety Authority. *EFSA Journal* 15 (1):4655, 53.
EFSA. 2016b. Scientific opinion on the appropriateness to set a group health-based guidance value for zearalenone and its modified forms. European Food Safety Authority. *EFSA Journal* 14 (4):4425, 46.
EFSA. 2004. Scientific opinion on the health risks to consumers associated with exposure to organotins in foodstuffs. European Food Safety Authority. *EFSA Journal* 102:119.
EFSA. 2017j. Scientific opinion on the re-evaluation of sodium nitrate (E 251) and potassium nitrate (E 252) as food additives. European Food Safety Authority. *EFSA Journal* 15 (6):4787, 123.
EFSA. 2018g. Scientific opinion on the risk for animal and human health related to the presence of dioxins and dioxin-like PCBs in feed and food. *EFSA Journal* 16 (11):5333, 331.
EFSA. 2011b. Scientific opinion on the risks for animal and public health related to the presence of *Alternaria* toxins in feed and food. European Food Safety Authority. *EFSA Journal* 9 (10):2407, 97.
EFSA. 2013c. Scientific opinion on the risks for animal and public health related to the presence of nivalenol in food and feed. European Food Safety Authority. *EFSA Journal* 11 (6):3262, 119.
EFSA. 2013d. Scientific opinion on the risks for animal and public health related to the presence of sterigmatocystin in feed and food. European Food Safety Authority. *EFSA Journal* 11 (6):3254, 81.
EFSA. 2011g. Scientific opinion on the risks for animal and public health related to the presence of T-2 and HT-2 toxin in food and feed. European Food Safety Authority. *EFSA Journal* 9 (12):2481, 187.

EFSA. 2018k. Scientific opinion on the risks for animal health related to the presence of fumonisins, their modified forms and hidden forms in feed. European Food Safety Authority. *EFSA Journal* 16 (5):5242, 144.

EFSA. 2017g. Scientific opinion on the risks for animal health related to the presence of zearalenone and its modified forms in feed. European Food Safety Authority. *EFSA Journal* 15 (7):4851, 123.

EFSA. 2014d. Scientific opinion on the risks for human and animal health related to the presence of modified forms of certain mycotoxins in food and feed. European Food Safety Authority. *EFSA Journal* 12 (12):3916, 107.

EFSA. 2016a. Scientific opinion on the risks for human health related to the presence of 3- and 2-monochloropropanediol (MCPD), and their fatty acid esters, and glycidyl fatty acid esters in food. European Food Safety Authority. *EFSA Journal* 14 (5):4426, 159.

EFSA. 2017i. Scientific statement on the risks for human health related to the presence of pyrrolizidine alkaloids in honey, tea, herbal infusions and food supplements. European Food Safety Authority. *EFSA Journal* 15 (7):4908, 34.

EFSA. 2012a. Scientific opinion on the risk for public health related to the presence of mercury and methylmercury in food. European Food Safety Authority. *EFSA Journal* 10 (12):2985, 241.

EFSA. 2015e. Scientific opinion on the risks for public health related to the presence of chlorate in food. European Food Safety Authority. *EFSA Journal* 13 (6):4135, 103.

EFSA. 2017c. Scientific opinion on the risks for public health related to the presence of furan and methylfurans in food. European Food Safety Authority. *EFSA Journal* 15 (10):5005, 142.

EFSA. 2011j. Scientific opinion on the risks for public health related to the presence of opium alkaloids in poppy seeds. European Food Safety Authority. *EFSA Journal* 9 (11):2405, 150.

EFSA. 2017a. Scientific opinion on the risks for public health related to the presence of tetrodotoxin (TTX) and TTX analogues in marine bivalves and gastropods. European Food Safety Authority. *EFSA Journal* 15 (4):4752, 65.

EFSA. 2011h. Scientific opinion on the risks for public health related to the presence of zearalenone in food. European Food Safety Authority. *EFSA Journal* 9 (6):2197, 124.

EFSA. 2012g. Scientific opinion on the risks to human and animal health related to the presence of citrinin in food and feed. European Food Safety Authority. *EFSA Journal* 10 (3):2605, 82.

EFSA. 2014f. Scientific opinion on the risks to human and animal health related to the presence of beauvericin and enniatins in food and feed. European Food Safety Authority. *EFSA Journal* 12 (8): 3802, 174.

EFSA. 2017d. Scientific opinion on the risks to human and animal health related to the presence of deoxynivalenol and its acetylated and modified forms in food and feed. European Food Safety Authority. *EFSA Journal* 15 (9):4718, 345.

EFSA. 2018l. Scientific opinion on the risks to human and animal health related to the presence of moniliformin in food and feed. European Food Safety Authority. *EFSA Journal* 16 (3):5082, 95.

EFSA. 2018m. Scientific opinion on the risk to human and animal health related to the presence of 4,15-diacetoxyscirpenol in food and feed. *EFSA Journal* 16 (8):5367, 106.

EFSA. 2018h. Scientific opinion on the risk to human health related to the presence of perfluoro octane sulfonic acid and perfluoro octanoic acid in food. *EFSA Journal* 16 (12):5194, 284.

EFSA. 2011c. Scientific opinion on the risk to public health related to the presence of high levels of dioxins and dioxin-like PCBs in liver from sheep and deer. European Food Safety Authority. *EFSA Journal* 9 (7):2297, 71.

EFSA. 2015f. Scientific opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs: Executive summary. *EFSA Journal* 13 (1):3978, 23.

EFSA. 2014a. Scientific opinion on the risks to public health related to the presence of chromium in food and drinking water. European Food Safety Authority. *EFSA Journal* 12 (3):3595, 261.

EFSA. 2015d. Scientific opinion on the risks to public health related to the presence of nickel in food and drinking water. European Food Safety Authority. *EFSA Journal* 13 (2):4002, 202.

EFSA. 2018i. Scientific opinion on the update of the risk assessment on 3-monochloropropane diol and its fatty acid esters. European Food Safety Authority. *EFSA Journal* 16 (1):5083, 48.

EFSA. 2006a. Scientific opinion related to ochratoxin a in food. European Food Safety Authority. *EFSA Journal* 4 (365):56.

EFSA. 2007b. Scientific opinion related to the potential increase of consumer health risk by a possible increase of the existing maximum levels for aflatoxins in almonds, hazelnuts and pistachios and derived products. European Food Safety Authority. *EFSA Journal* 5 (446):127.

EFSA. 2005b. Scientific opinion related to the presence of non-dioxin-like polychlorinated biphenyls (PCB) in feed and food. European Food Safety Authority. *EFSA Journal* 284:137.

EFSA. 2017h. Scientific report on human and animal dietary exposure to ergot alkaloids. European Food Safety Authority. *EFSA Journal* 15 (7):4902, 53.

EFSA. 2017f. Scientific report on human and animal dietary exposure to T-2 and HT-2 toxin. European Food Safety Authority. *EFSA Journal* 15 (8):4972, 57.

EFSA. 2016c. Scientific report on the dietary exposure assessment to *Alternaria* toxins in the European population. European Food Safety Authority. *EFSA Journal* 14 (12):4654, 32.

EFSA. 2018b. Scientific report on the occurrence of residues of fipronil and other acaricides in chicken eggs and poultry muscle/fat. *EFSA Journal* 16 (5):5164, 30.

EFSA. 2010f. Scientific statement on further elaboration of the consumption figure of 400 g shellfish meat on the basis of new consumption data. European Food Safety Authority. *EFSA Journal* 8 (8):1706, 20.

EFSA. 2009j. Scientific statement on processing on the levels of lipophilic marine biotoxins in bivalve molluscs. European Food Safety Authority. *EFSA Journal* 1016:10.

EFSA. 2010d. Scientific statement on recent scientific information on the toxicity of ochratoxin A. European Food Safety Authority. *EFSA Journal* 8:1626, 7.

EFSA. 2015a. Scientific statement on the benefits of fish/seafood consumption compared to the risks of methylmercury in fish/seafood. European Food Safety Authority. *EFSA Journal* 13 (1):3982, 36.

EFSA. 2018j. Scientific statement on the effect on public health of a possible increase of the maximum level for 'aflatoxin total' from 4 to 10 μg/kg in peanuts and processed products thereof, intended for direct human consumption or use as an ingredient in foodstuffs. European Food Safety Authority. *EFSA Journal* 16 (2):5175, 32.

EFSA. 2015c. Scientific statement on the health-based guidance value for dioxins and dioxin-like PCBs. European Food Safety Authority. *EFSA Journal* 13 (5):4124, 14.

EFSA. 2016f. Scientific statement on the presence of microplastics and nanoplastics in food, with particular focus on seafood. European Food Safety Authority. *EFSA Journal* 14 (6):4501, 30.

EFSA. 2013e. Scientific statement on the risks for public health related to a possible increase of the maximum level of deoxynivalenol for certain semi-processed cereal products. European Food Safety Authority. *EFSA Journal* 11 (12):3490, 56.

EFSA. 2009a. Statement of EFSA on the risks for public health due to the presence of dioxins in pork from Ireland. European Food Safety Authority. *EFSA Journal* 911:15.

EFSA 2009c. Scientific opinion on arsenic in food. *EFSA Journal* 7 (10):1351.

EFSA. 2011a. Shiga toxin-producing *E. coli* (STEC) O104:H4 2011 outbreaks in Europe: Taking stock. *European Food Safety Authority. EFSA Journal* 9:2390.

EFSA. 2008d. Statement of EFSA on risks for public health due to the presences of melamine in infant milk and other milk products in China. European Food Safety Authority. *EFSA Journal* 807:10.

EFSA. 2019b. Statement of EFSA on the genotoxicity assessment of chemical mixtures. *EFSA Journal* 17 (1):5519, 11.

EFSA. 2017k. The 2015 European Union report on pesticide residues in food. European Food Safety Authority. *EFSA Journal* 15 (4):4791, 134.

EFSA. 2012b. Update of the monitoring of dioxins and PCBs levels in food and feed. European Food Safety Authority. *EFSA Journal* 10: 2832, 82.

EFSA. 2018n. Update of the scientific opinion on opium alkaloids in poppy seeds. European Food Safety Authority. *EFSA Journal* 16 (5): 5243, 119.

EFSA and ECDC. 2018a. Multi-country outbreak of Listeria monocytogenes serogroup IVb, multi-locus sequence type 6, infections linked to frozen corn and possibly to other frozen vegetables – first update. European Food Safety Authority. *EFSA Supporting Publication* 2018: EN-1448, 19.

EFSA and ECDC. 2018b. The European union summary report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in 2016. European Food Safety Authority. *EFSA Journal* 16 (2):5182, 270.

EFSA and ECDC. 2017. The European union summary report on trends and sources of zoonoses, zoonotic agents and food-borne outbreaks in 2016. European Food Safety Authority. *EFSA Journal* 15 (12):5077, 228.

Ekart, K., A. Hmelak Gorenjak, E. Madorran, S. Lapajne, and T. Langerholc. 2013. Study on the influence of food processing on nitrate levels in vegetables. European Food Safety Authority. *EFSA Supporting Publication* 2013:EN-514, 150.

EMA. 2018. European Medicines Agency. Veterinary medicines: regulatory information. Accessed 17 May 2018. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/landing/veterinary_medicines_regulatory.jsp&mid=.

EP and Council. 2004. Regulation (EC) no 853/2004 of the European Parliament and of the Council of 29 April 2004 laying down specific hygiene rules for food of animal origin. *Official Journal of the European Union* L226:22–82.

EP and Council. 2002. Regulation (EC) no 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. *Official Journal of the European Communities* L31:1–24.

Eriksen, K. T., O. Raaschou-Nielsen, J. K. McLaughlin, L. Lipworth, A. Tjønneland, K. Overvad, and M. Sørensen. 2013. Association between plasma PFOA and PFOS levels and total cholesterol in a Middle-aged Danish population. *PLoS One* 8 (2):e56969. doi: 10.1371/journal.pone.0056969.

Eriksson, J., N. Green, G. Marsh, and A. Bergman. 2004. Photochemical decomposition of 15 polybrominated diphenyl ether congeners in methanol/water. *Environmental Science & Technology* 38 (11):3119–25.

Eskola, M., A. Altieri, and J. Galobart. 2018. Overview of the activities of the European Food Safety Authority on mycotoxins in food and feed. *World Mycotoxin Journal* 11 (2):277–89. doi: 10.3920/WMJ2017.2270.

EU Food Policy. 2018. Council conclusions link obesity to eating more processed food. Issue no. 430 June 15, 2018.

Eurostat. 2018. Statistics explained. Overweight and obesity – BMI statistics. Accessed 22 June 2018. http://ec.europa.eu/eurostat/statistics-explained/index.php/Overweight_and_obesity_-_BMI_statistics#Main_statistical_findings.

FAO. 2015. The State of Agricultural Commodity Markets 2015-2016. Trade and food security: achieving a better balance between national priorities and the collective good. Food and Agriculture Organization of the United Nations, Rome. Accessed 19 April 2018. http://www.fao.org/publications/soco/the-state-of-agricultural-commodity-markets-2015-16/en/.

Ferreccio, C., C. Gonzalez, V. Milosavjlevic, G. Marshall, A. M. Sancha, and A. H. Smith. 2000. Lung cancer and arsenic concentrations in drinking water in Chile. *Epidemiology* 11 (6):673–9. doi: 10.1097/00001648-200011000-00010.

Frewer, L. J., K. Bergmann, M. Brennan, R. Lion, R. Meertens, G. Rowe, M. Siegrist, and C. Vereijken. 2011. Consumer response to novel agri-food technologies: Implications for predicting consumer acceptance of emerging food technologies. *Trends in Food Science & Technology* 22:442–56. doi: 10.1016/j.tifs.2011.05.005.

Frewer, L. J., A. R. H. Fischer, M. Brennan, D. Bánáti, R. Lion, R. M. Meertens, G. Rowe, M. Siegrist, W. Verbeke and C. M. J. L. Vereijken. 2016. Risk/Benefit Communication about Food—A Systematic Review of the Literature. *Critical Reviews in Food Science and Nutrition* 56 (10):1728–1745. doi: 10.1080/10408398.2013.801337.

FSA. 2017. Communicating with the public on chemical contaminants. Research report Kantar Public – March 2017. UK Food Standards Agency. Accessed 17 June 2018. https://acss.food.gov.uk/sites/default/files/chemicalscontaminants.pdf.

FSAI. 2019. Healthy eating, food safety and food legislation. A guide supporting the healthy Ireland food pyramid. https://www.fsai.ie/science_and_health/healthy_eating.html.

Gallagher, C. M., J. S. Kovach, and J. R. Meliker. 2008. Urinary cadmium and osteoporosis in U.S. Women ≥50 years of age: NHANES 1988–1994 and 1999–2004. *Environmental Health Perspectives* 116 (10):1338–43. doi: 10.1289/ehp.11452.

Hartmann, C., S. Hieke, C. Taper, and M. Siegrist. 2018. European consumer healthiness evaluation of free-'from' labelled food products. *Food Quality and Preference* 68:377–88. doi: 10.1016/j.foodqual.2017.12.009.

IARC. 2010b. Alcohol consumption and ethyl carbamate. IARC monographs on the evaluation of carcinogenic risks to humans, volume 96. World Health Organization International Agency for Research on Cancer (IARC), Lyon, France.

IARC. 2012. Chemical agents and related occupations. A review of human carcinogens. IARC monographs on the evaluation of carcinogenic risks to humans, volume 100 F. World Health Organization International Agency for Research on Cancer (IARC), Lyon, France.

IARC. 2004. Cruciferous vegetables, isothiocyanates and indoles. IARC Handbooks of Cancer Prevention, International Agency for Research on Cancer, Lyon, France.

IARC. 2003. Fruit and vegetables. IARC handbooks of cancer prevention. International Agency for Research on Cancer, Lyon.

IARC. 2018. Red meat and processed meat. Volume 114. IARC monographs. IARC monographs on the evaluation of carcinogenic risks to humans. International Agency for Research on Cancer, World Health Organization, Lyon, France.

IARC. 2010a. Some non-heterocyclic polycyclic aromatic hydrocarbons and some related exposures. IARC monographs on the evaluation of carcinogenic risks to humans, volume 92. World Health Organization International Agency for Research on Cancer (IARC), Lyon, France.

IARC. 2014. World Cancer Report 2014. World Cancer Reports, eds. B.W. Stewart and C.O. Wild. International Agency for Research on Cancer, World Health Organization. Lyon, France.

IARC 2008. World Cancer Report 2008. World Cancer Reports, eds. P. Boyle and B Levin. International Agency for Research on Cancer, World Health Organization. Lyon, France.

ICF and GfK. 2018. EU insights – consumer perceptions of emerging risks in the food chain. European Food Safety Authority. *EFSA Supporting Publication* 2018:EN-1394, 81.

Ingram, A. J., J. C. Phillips, and S. Davies. 2000. DNA adducts produced by oils, oil fractions and polycyclic aromatic hydrocarbons in relation to repair processes and skin carcinogenesis. *Journal of Applied Toxicology* 20 (3):165–74. doi: 10.1002/(SICI)1099-1263(200005/06)20:3<165::AID-JAT625>3.0.CO;2-E.

IPCS. 2009. Principles and methods for the risk assessment of chemicals in food. A joint publication of the Food and Agriculture Organization of the United Nations and the World Health Organization. Environmental Health Criteria 240.

Janić Hajnal, E., J. Kos, J. Krulj, S. Krstović, I. Jajić, L. Pezo, B. Šarić, and N. Nedeljković. 2017. Aflatoxins contamination of maize in Serbia: The impact of weather conditions in 2015. *Food Additives* *and Contaminants Part A* 34 (11):1999–2010. doi: 10.1080/19440049.2017.1331047.

JECFA. 2017. Evaluation of certain contaminants in food. Eighty-third report of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Food and Agriculture Organization of the United Nations, World Health Organization, WHO Technical Report Series 1002. World Health Organization, Geneva.

JECFA. 2002. Evaluation of certain food additives and contaminants. Fifty-seventh report of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). WHO Technical Report series, 909.

JECFA. 1999. Evaluation of certain food additives and contaminants. Forty-sixth report of Joint FAO/WHO Expert Committee on Food Additives (JECFA). Food and Agriculture Organization of the United Nations, World Health Organization, WHO Technical Report Series 884. World Health Organization, Geneva.

JECFA. 2011. Safety evaluation of certain contaminants in food. Prepared by the Seventy-second meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). WHO Food Additives Series 63, FAO JECFA Monographs 8. World Health Organization (WHO), Geneva, Food and Agriculture Organization of the United Nations (FAO), Rome.

JECFA. 2006. Safety evaluation of certain contaminants in food. Prepared by the Sixty-fourth meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). WHO Food Additives Series: 55; FAO Food and Nutrition Paper 82; World Health Organization WHO, Food and Agriculture Organization of the United Nations FAO.

JECFA. 2008. Safety evaluation of certain food additives and contaminants. Prepared by the Sixty-eighth meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). JECFA Monographs. Food and Agriculture Organization of the United Nations, World Health Organization, IPCS – International Programme on Chemical Safety, WHO Food Additives Series No. 59, World Health Organization, Geneva.

JECFA. 2016. Safety evaluation of certain food additives and contaminants. Supplement 1: Non-dioxin-like polychlorinated biphenyls. Prepared by the eightieth meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). WHO Food Additives Series: 71-S1.

JECFA. 2001. Safety evaluation of certain mycotoxins in food. Prepared by the Fifty-sixth meeting of the Joint FAO/WHO Expert Committee in Food Additives (JECFA). JECFA Monographs. Food and Agriculture Organization of the United Nations, World Health Organization, IPCS – International Programme on Chemical Safety, WHO Food Additives Series No. 47, FAO Food and Nutrition Paper 74.

Jin, T., G. Nordberg, T. Ye, M. Bo, H. Wang, G. Zhu, Q. Kong, and A. Bernard. 2004. Osteoporosis and renal dysfunction in a general population exposed to cadmium in China. *Environmental Research* 96 (3):353–9. doi: 10.1016/j.envres.2004.02.012.

Karagas, M. R., T. A. Stukel, and T. D. Tosteson. 2002. Assessment of cancer risk and environmental levels of arsenic in New Hampshire. *International Journal of Hygiene and Environmental Health* 205 (1–2):85–94. doi: 10.1078/1438-4639-00133.

Karagas, M. R., T. D. Tosteson, J. S. Morris, E. Demidenko, L. A. Mott, J. Heaney, and A. Schned. 2004. Incidence of transitional cell carcinoma of the bladder and arsenic exposure in New Hampshire. *Cancer Causes & Control : CCC* 15 (5):465–72. doi: 10.1023/B:CACO.0000036452.55199.a3.

Krska, R., M. de Nijs, O. McNerney, M. Pichler, J. Gilbert, S. Edwards, M. Suman, N. Magan, V. Rossi, H. J. van der Fels-Klerx, et al. 2016. Safe food and feed through an integrated toolbox for mycotoxin management: the MyToolBox approach. *World Mycotoxin Journal* 9 (4):487–95. doi: 10.3920/WMJ2016.2136.

Kortenkamp, A., T. Backhaus, and M. Faust. 2009. State of the art report on mixture toxicity. Final report. Executive summary. 22 December 2009. European Commission. Accessed 18 October 2018. http://ec.europa.eu/environment/chemicals/effects/pdf/report_mixture_toxicity.pdf.

Kos, J., J. Mastilović, E. Janić Hajnal, and B. Šarić. 2013. Natural occurrence of aflatoxins in maize harvested in Serbia during 2009-2012. *Food Control* 34 (1):31–4. doi: 10.1016/j.foodcont.2013.04.004.

Lanphear, B. P., R. Hornung, J. Khoury, K. Yolton, P. Baghurst, D. C. Bellinger, R. L. Canfield, K. N. Dietrich, R. Bornschein, T. Greene, et al. 2005. Low-level environmental lead exposure and children's intellectual function: an international pooled analysis. *Environmental Health Perspectives* 113 (7):894–9. doi: 10.1289/ehp.7688.

López, P., M. de Nijs, M. Spanjer, A. Pietri, T. Bertuzzi, A. Starski, J. Postupolski, M. Castellari, and M. Hortós. 2017. Generation of occurrence data on citrinin in food. European Food Safety Authority. *EFSA Supporting Publication* 2017:EN-1177, 47.

Mackerer, C. R., L. C. Griffis, J. S. Grabowski, Jr, and F. A. Reitman. 2003. Petroleum mineral oil refining and evaluation of cancer hazard. *Applied Occupational and Environmental Hygiene* 18 (11):890–901. doi: 10.1080/10473220390237467.

Maranghi, F., R. Tassinari, L. Narciso, S. Tait, C. La Rocca, G. Di Felice, C. Butteroni, S. Corinti, B. Barletta, E. Cordelli., et al. 2018. *In vivo* toxicity and genotoxicity of beauvericin and enniatins. Combined approach to study in vivo toxicity and genotoxicity of mycotoxins beauvericin (BEA) and enniatin B (ENNB). *EFSA Supporting Publication* 2018:EN-1406, 183.

Marvin, H. J. P. 2012. EMTOX: Climate change impacts on natural toxins in marine and primary plant production system in North West Europe by 2040. *Food Additives and Contaminants Part A* 29 (10):1501. doi: 10.1080/19440049.2012.724889.

McEvoy, J. D. G. 2016. Emerging food safety issues: an EU perspective. *Drug Testing and Analysis* 8 (5-6):511–520. doi: 10.1002/dta.2015.

Mínguez-Alarcón, L., O. Sergeyev, J. S. Burns, P. L. Williams, M. M. Lee, S. A. Korrick, L. Smigulina, B. Revich, and R. Hauser. 2017. A longitudinal study of peripubertal serum organochlorine concentrations and semen parameters in young men: the Russian Children's Study. *Environmental Health Perspectives* 125 (3):460–466. doi: 10.1289/EHP25.

Mol, H. G. J., A. Pietri, S. J. MacDonald, C. Anagnostopoulos, and M. Spanjer. 2015. Survey on sterigmatocystin in food. European Food Safety Authority. *EFSA Supporting Publication* 2015:EN-774, 56.

Moser, G. J., J. Foley, M. Burnett, T. L. Goldsworthy, and R. Maronpot. 2009. Furan-induced dose-response relationships for liver cytotoxicity, cell proliferation, and tumorigenicity (furan-induced liver tumorigenicity). *Experimental and Toxicologic Pathology* 61 (2):101–111. doi: 10.1016/j.etp.2008.06.006.

Mulder, P. P. J., M. De Nijs, M. Castellari, M. Hortos, S. MacDonald, C. Crews, J. Hajslova, and M. Stranska. 2016. Occurrence of tropane alkaloids in food. European Food Safety Authority. *EFSA Supporting Publication* 2016:EN-1140, 200.

Naustvoll, L.-J., E. Gustad, and E. Dahl. 2012. Monitoring of *Dinophysis* species and diarrhetic shellfish toxins in Flødevigen Bay, Norway: Inter-annual variability over a 25-year time-series. *Food Additives and Contaminants Part A* 29 (10):1605–1615. doi: 10.1080/19440049.2012.714908.

Navas-Acien, A., M. Tellez-Plaza, E. Guallar, P. Muntner, E. Silbergeld, B. Jaar, and V. Weaver. 2009. Blood cadmium and lead and chronic kidney disease in US adults: a joint analysis. *American Journal of Epidemiology* 170 (9):1156–1164. doi: 10.1093/aje/kwp248.

NCTR. 2015. Two-year carcinogenicity bioassay of furan in F344 rats. Technical report for National Center for Toxicological Research (NCTR) experiment No E2168.01, Test No. E2168.02, 102 pp.

Nelson, J. W., E. E. Hatch, and T. F. Webster. 2010. Exposure to polyfluoroalkyl chemicals and cholesterol, body weight, and insulin resistance in the general U.S. population. *Environmental Health Perspectives* 118 (2):197–202. doi: 10.1289/ehp.0901165.

Niinemets, Ü., A. Kahru, P. Nõges, A. Tuvikene, A. Vasemägi, Ü. Mander, and T. Nõges. 2017. Environmental feedbacks in temperate aquatic ecosystems under global change: why do we need to consider chemical stressors? *Regional Environmental Change* 17 (7):2079–2096. doi: 10.1007/s10113-017-1197-2.

NTP. 1993a. US National Toxicology Program (NTP), Perinatal toxicology and carcinogenesis studies of polybrominated biphenyls (Firemaster FF-1) (CAS No. 67774-32-7) in F344/N rats and

B6C3F1 mice (feed studies). US Department of Health and Human Services, NTP Technical Report Series 398, National Institutes of Health Publication No. 92-2853.

NTP. 2012. US National Toxicology Program (NTP), Toxicology and carcinogenesis studies of acrylamide (CAS No. 79-06-1) in F344/N rats and B6C3F1 mice (feed and drinking water studies). US Department of Health and Human Services, NTP Technical Report Series 575, National Institutes of Health Publication No. 12-5917.

NTP. 2010. US National Toxicology Program (NTP), Toxicology and carcinogenesis studies of chromium picolinate monohydrate (CAS No. 27882-76-4) in F344/N rats and B6C3F1 mice (feed studies). US Department of Health and Human Services, NTP Technical Report Series, No. 556, National Institutes of Health Publication No. 10-5897.

NTP. 1993b. US National Toxicology Program (NTP), Toxicology and carcinogenesis studies of furan (CAS No. 110-00-9) in F344 rats and B6C3F1 mice (gavage studies). US Department of Health and Human Services, NTP Technical Reports Series, No. 402. National Institutes of Health Publication No. 93-2857

NTP. 1990. US National Toxicology Program (NTP), Toxicology and carcinogenesis studies of glycidol (CAS No. 556-52-5) in F344/N rats and B6C3F1 mice (gavage studies). US Department of Health and Human Services, NTP Technical Report Series No. 374, National Institutes of Health Publication No. 90-2829.

NTP. 2003. US National Toxicology Program (NTP), Toxicology and carcinogenesis studies of riddelliine (CAS NO. 23246-96-0) in F344/N rats and B6C3F1 mice (gavage studies). US Department of Health and Human Services, NTP Technical Report Series No. 508, National Institutes of Health Publication No. 03-4442.

NTP. 2004. US National Toxicology Program (NTP), Toxicology and carcinogensis studies of urethane, ethanol, and urethane/ethanol (urethane, CAS No. 51-79-6; ethanol, CAS No. 64-17-5) in B6C3F1 mice (drinking water studies). US Department of Health and Human Services, NTP Technical Report Series No. 510:1-346. National Institutes of Health Publication No. 04-4444.

OECD. 2005. Organisation for Economic Co-operation and Development (OECD). 2,4,6- ribromophenol CAS No: 118-79-6. Screening Information Data Set (SIDS) Initial Assessment Report for SIAM 17.

Parikka, P., K. Hakala, and K. Tiilikkala. 2012. Expected shifts in Fusarium species' composition on cereal grain in Northern Europe due to climatic change. *Food Additives and Contaminants Part A* 29 (10):1543–1555. doi: 10.1080/19440049.2012.680613.

Reynolds, A., J. Mann, J. Cummings, N. Winter, E. Mete, and L. T. Morenga. 2019. Carbohydrate quality and human health: A series of systematic reviews and meta-analyses. *The Lancet* 393 (10170): 434–45. doi: 10.1016/S0140-6736(18)31809-9.

Rice, D. C., E. A. Reeve, A. Herlihy, R. T. Zoeller, W. D. Thompson, and V. P. Markowski. 2007. Developmental delays and locomotor activity in the C57BL6/J mouse following neonatal exposure to the fully-brominated PBDE, decabromodiphenyl ether. *Neurotoxicology and Teratology* 29 (4):511–520. doi: 10.1016/j.ntt.2007.03.061.

Schneider, K., R. Roller, F. Kalberlah, and U. Schuhmacher-Wolz. 2002. Cancer risk assessment for oral exposure to PAH mixtures. *Journal of Applied Toxicology* 22 (1):73–83.

Schutte, R., T. S. Nawrot, T. Richart, L. Thijs, D. Vanderschueren, T. Kuznetsova, E. Van Hecke, H. A. Roels, and J. A. Staessen. 2008. Bone resorption and environmental exposure to cadmium in women: a population study. *Environmental Health Perspectives* 116 (6):777–783. doi: 10.1289/ehp.11167.

Selmer, R. M., I. S. Kristiansen, A. Haglerod, S. Graff-Iversen, H. K. Larsen, H. E. Meyer, K. H. Bonaa, and D. S. Thelle. 2000. Cost and health consequences of reducing the population intake of salt. *Journal of Epidemiology & Community Health* 54 (9):697–702. doi: 10.1136/jech.54.9.697.

SLI. 2000a. A one-generation reproduction range-finding study in rats with nickel sulfate hexahydrate. Spencerville, OH: Springborn Laboratories (SLI), Inc. SLI Study No. 3472.3.

SLI. 2000b. An oral (gavage) two-generation reproduction toxicity study in Sprague-Dawley rats with nickel sulfate hexahydrate. Final Report. Volume 1 of 3. Spencerville, OH: Springborn Laboratories (SLI), Inc. SLI Study No. 3472.4.

Smith, J. H., A. K. Mallett, R. A. Priston, P. G. Brantom, N. R. Worrell, C. Sexsmith, and B. J. Simpson. 1996. Ninety-day feeding study in Fischer-344 rats of highly refined petroleum-derived food-grade white oils and waxes. *Toxicologic Pathology* 24 (2):214–230. doi: 10.1177/019262339602400210.

Staessen, J. A., H. A. Roels, D. Emelianov, T. Kuznetsova, L. Thijs, J. Vangronsveld, and R. Fagard. 1999. Environmental exposure to cadmium, forearm bone density, and risk of fractures: prospective population study. Public Health and Environmental Exposure to Cadmium (PheeCad) Study Group. *The Lancet* 353 (9159): 1140–1144. doi: 10.1016/S0140-6736(98)09356-8.

Steenland, K., S. Tinker, S. Frisbee, A. Ducatman, and V. Vaccarino. 2009. Association of perfluorooctanoic acid and perfluorooctane sulfonate with serum lipids among adults living near a chemical plant. *American Journal of Epidemiology* 170 (10):1268–1278. doi: 10.1093/aje/kwp279.

Tam, C., T. Larose, and S.J. O'Brien. 2014. Costed extension to the second study of infectious intestinal disease in the community: Identifying the proportion of foodborne disease in the UK and attributing foodborne disease by food commodity. Project B18021 (FS231043). Funder: UK Food Standards Agency (UK FSA). Accessed 9 September 2018. https://www.food.gov.uk/sites/default/files/media/document/IID2%20extension%20report%20-%20FINAL%2025%20March%202014.pdf.

Testai, E., F. M. Buratti, E. Funari, M. Manganelli, S. Vichi, N. Arnich, R. Biré, V. Fessard, and A. Sialehaamoa. 2016. Review and analysis of occurrence, exposure and toxicity of cyanobacteria toxins in food. European Food Safety Authority. *EFSA Supporting Publication* 2016:EN-998, 309.

Thomson, B., and M. Rose. 2011. Environmental contaminants in foods and feeds in the light of climate change. *Quality Assurance and Safety of Crops & Foods* 3:2–11. doi: 10.1111/j.1757-837X.2010.00086.x.

Van der Fels-Klerx, H., J. E. Olesen, L.-J. Naustvoll, Y. Friocourt, M. Mengelers, and J. Christensen. 2012a. Climate change impacts on natural toxins in food production systems, exemplified by deoxynivalenol in wheat and diarrhetic shellfish toxins. *Food Additives and Contaminants Part A* 29 (10):1647–1659. doi: 10.1080/19440049.2012.714080.

Van der Fels-Klerx, H., J. E. Olesen, M. Madsen, and P. Goedhart. 2012b. Climate change increases deoxynivalenol contamination of wheat in North-Western Europe. *Food Additives and Contaminants Part A* 29 (10):1593–1604. doi: 10.1080/19440049.2012.691555.

Van der Fels-Klerx, H. J., C. Liu, and P. Battilani. 2016. Modelling climate change impacts on mycotoxin contamination. *World Mycotoxin Journal* 9 (5):717–726. doi: 10.3920/WMJ2016.2066.

Van der Ven, L. T. M., T. Van de Kuil, A. Verhoef, C. M. Verwer, H. Lilienthal, P. E. G. Leonards, U. M. D. Schauer, R. F. Cantón, S. Litens, F. H. De Jong, et al. 2008. Endocrine effects of tetrabromobisphenol-A (TBBPA) in Wistar rats as tested in a one-generation reproduction study and a subacute toxicity study. *Toxicology* 245 (1–2):76–89. doi: 10.1016/j.tox.2007.12.009.

Van der Ven, L., A. Verhoef, T. van de Kuil, W. Slob, P. E. G. Leonards, T. J. Visser, T. Hamers, M. Herlin, H. Håkansson, H. Olausson., et al. 2006. A 28-day oral dose toxicity study enhanced to detect endocrine effects of hexabromocyclododecane in Wistar rats. *Toxicological Sciences* 94 (2):281–292. doi: 10.1093/toxsci/kfl113.

Viberg, H., A. Fredriksson, and P. Eriksson. 2007. Changes in spontaneous behaviour and altered response to nicotine in the adult rat, after neonatal exposure to the brominated flame retardant, decabrominated diphenyl ether (PBDE 209). *Neurotoxicology* 28 (1): 136–142. doi: 10.1016/j.neuro.2006.08.006.

Viberg, H., A. Fredriksson, and P. Eriksson. 2004. Neonatal exposure to the brominated flame-retardant, 2,2',4,4',5-pentabromodiphenyl ether, decreases cholinergic nicotinic receptors in hippocampus and affects spontaneous behaviour in the adult mouse. *Environmental Toxicology and Pharmacology* 17 (2):61–65. doi: 10.1016/j.etap.2004.02.004.

Von Tungeln, L. S., N. J. Walker, G. R. Olson, M. C. Mendoza, R. P. Felton, B. T. Thorn, M. M. Marques, I. P. Pogribny, D. R. Doerge, and F. A. Beland. 2017. Low dose assessment of the carcinogenicity of furan in male F344/N Nctr rats in a 2-year gavage study. *Food and Chemical Toxicology* 99:170–181. doi: 10.1016/j.fct.2016.11.015.

Wang, H., G. Zhu, Y. Shi, S. Weng, T. Jin, Q. Kong, and G. F. Nordberg. 2003. Influence of environmental cadmium exposure on forearm bone density. *Journal of Bone and Mineral Research* 18 (3): 553–560. doi: 10.1359/jbmr.2003.18.3.553.

WHO. 2014. Antimicrobial Resistance. Global Report on surveillance 2014. World Health Organization. Accessed 2 June 2018. http://www.who.int/drugresistance/documents/surveillancereport/en/.

WHO. 2003. Diet, nutrition and the prevention of chronic diseases. Report of the joint WHO/FAO expert consultation. Technical Report Series, No. 916. World Health Organization, Geneva.

WHO Europe. 2018. Obesity. WHO Regional Office for Europe. Accessed 15 June 2018. http://www.euro.who.int/en/health-topics/noncommunicable-diseases/obesity.

WHO. 2011. Global status report on noncommunicable diseases 2010. World Health Organization, 161 pp.

WHO. 2018. Obesity and overweight. World Health Organization. Accessed 15 June 2018. http://www.who.int/en/news-room/fact-sheets/detail/obesity-and-overweight.

WHO. 2006. Principles for evaluating health risks in children associated with exposure to chemicals. Environmental Health Criteria 237. World Health Organization.

WHO. 2002. The World Health Report. Reducing risks, promoting healthy life. Accessed 14 June 2018. http://www.who.int/whr/2002/en/Overview_E.pdf

Wild, C. P. 2012. The exposome: from concept to utility. *International Journal of Epidemiology* 41: 24–32.

Willett, W., J. Rockström, B. Loken, M. Springmann, T. Lang, S. Vermeulen, T. Garnett, D. Tilman, F. DeClerck, A. Wood, et al. 2019. Food in the Anthropocene: The EAT-Lancet Commission on healthy diets from sustainable food systems. *The Lancet* 393 (10170):447–92. doi: 10.1016/S0140-6736(18)31788-4.

Xia, Y., T. J. Wade, K. Wu, Y. Li, Z. Ning, X. C. Le, X. He, B. Chen, Y. Feng, and J. L. Mumford. 2009. Well water arsenic exposure, arsenic induced skin-lesions and self-reported morbidity in Inner Mongolia. *International Journal of Environmental Research and Public Health* 6 (3):1010–1025. doi: 10.3390/ijerph6031010.

Yeh, F. S., M. C. Yu, C. C. Mo, S. Luo, M. J. Tong, and B. E. Henderson. 1989. Hepatitis B virus, aflatoxins, and hepatocellular carcinoma in Southern Guangxi, China. *Cancer Research* 49: 2506–2509.

Yoe, C. 2012. *Principles of risk analysis: Decision making under uncertainty*, 561. Boca Raton, FL: CRC Press.