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A vision on the 'foodture' role of dietary exposure sciences in the interplay between food safety and nutrition

Maryam Zare Jeddi [a], Polly E. Boon [a], Francesco Cubadda [b], Ron Hoogenboom [c], Hans Mol [c], Hans Verhagen [d,e], Dick T.H.M. Sijm [f,g,*]

[a] National Institute for Public Health and the Environment (RIVM), 3721 MA, Bilthoven, the Netherlands
[b] Istituto Superiore di Sanità - National Institute of Health, Viale Regina Elena 299, 00161, Rome, Italy
[c] Wageningen Food Safety Research, Wageningen University and Research, Akkermaalsbos 2, 6708 WB, Wageningen, the Netherlands
[d] Nutrition Innovation Center for Food and Health (NICHE), University of Ulster, Coleraine BT52 1SA, Northern Ireland, UK
[e] Technical University of Denmark, Lyngby, Denmark
[f] Office of Risk Assessment and Research, Netherlands Food and Product Safety Authority, 3540 AA, Utrecht, the Netherlands
[g] Maastricht University, the Netherlands

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ABSTRACT

Background: In this paper, the European chapter of the International Society for Exposure Science (ISES Europe) provides a vision on how dietary exposure sciences can contribute to address the challenges in the field of food safety and nutrition due to changes in food systems by answering the following question: How can we assess timely and accurately changes in dietary exposure to hazardous chemicals (and mixtures thereof) or intake of nutrients due to changes in food production, food consumption and food composition?
Scope and approach: We first describe the current role of dietary exposure sciences and the instruments that are being used to assess dietary exposure in food safety and nutrition. This is followed by an analysis of current changes and developments, primarily at the European level, relevant for food safety and nutrition. This results in a list of identified challenges for dietary exposure sciences.
Key findings and conclusions: We thus focus on the timely and accurate assessment of the impact of changes and developments on consumer's and public health, from the perspective of dietary exposure sciences. This includes making better use of chemical analysis, dietary exposure assessment and human biomonitoring, providing increased insight in food composition and nutrients, taking into account the impact of new technologies on human exposure, and making better use of risk-benefit assessment.

1. Introduction

Food safety is considered as a public health and socioeconomic priority. Nutrition and food safety are closely interlinked as two health outcomes from food systems (WHO, 2021). Provision of safe, nutritious and high-quality food will become more and more challenging in the next decades owing to changes in global food systems and those of the European Union (EU) (EU, 2020; WHO, 2021). These changes are driven by a combination of factors, such as climate change, the growing world population, migrations, urbanization, increased demand for animal protein, increased prosperity (need to produce more and better-quality food), resource scarcity and globalisation of the food supply (FAO, 2018; FAO IFAD UNICEF WFP & WHO, 2020; Govindan, 2018; Klosse, 2019; Knorr et al., 2018; Misiou & Koutsoumanis, 2021). All these factors contribute to major shifts in the way food is and will be produced, distributed and consumed worldwide, and will eventually alter food composition, dietary habits, and access to and availability and affordability of food (King et al., 2017; Webb et al., 2020). Although the transition to more sustainable food systems has started, existing food systems do not yet sufficiently address these challenges. Current production practices and consumption patterns still result in dietary exposure to residues from pesticides and veterinary drugs (EFSA, 2021h, 2021j) and new and emerging contaminants, such as natural toxins and environmental and processing contaminants, that may be detrimental

* Corresponding author. Office of Risk Assessment and Research, Netherlands Food and Product Safety Authority, P.O. Box 43006, 3540 AA, Utrecht, the Netherlands.
E-mail address: T.H.M.Sijm@nvwa.nl (D.T.H.M. Sijm).

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for health. This was recently shown for, e.g., dioxins and dl-PCBs (EFSA, 2018), PFASs (EFSA, 2020b), aflatoxins (EFSA, 2020a), and for bisphenol A (EFSA, 2021b, p. 78). Many contaminants are routinely monitored in the EU and evidence on their occurrence is contained in the respective EFSA Scientific Opinions.[1] Although in most cases the levels of individual contaminants are below the established maximum (residue) levels, some exceedances do occur. It should be considered that for contaminants, these maximum levels take into account the feasibility with respect to existing levels, aiming at reducing the levels in the longer term. This implies that MLs are often not at the level that would exclude exceedance of the health-based guidance values and thus protect consumer health, which especially applies when many products are relatively close to the MLs. The consumer is often exposed to multiple residues/contaminants and there is still a knowledge gap on possible effects of these combined exposures (hereafter called "mixtures") (Boberg et al., 2021).

Inefficient use of fertilisers, losses of nutrients from fertilisers, pollution of water, soil and air, and use of antimicrobials in animal production and aquaculture in many areas of the world are additional drawbacks negatively impacting the environment and human health (Agrimonti et al., 2021). At the same time, a sizeable proportion of food is lost or wasted from households, retail establishments and the food service industry, and unbalanced diets contribute to obesity and non-communicable diseases. Changes in food systems may introduce novel contaminants, making it challenging to ensure food safety (King et al., 2017). Although regulatory and monitoring efforts have been made over the years, and Europe has a high level of food safety, also European consumers are exposed to contaminants that have not yet been detected, studied or regulated (Eskola et al., 2020; Oltmanns et al., 2020). These unknown contaminants and emerging risks might pose a threat to human health. The same holds for combined exposure to multiple chemicals, which are difficult to characterise and whose concerted effects are difficult to predict (Flynn et al., 2019; Kahn et al., 2020; Muncke et al., 2020).

This paper focuses on food safety and nutrition in a changing environment from the perspective of hazardous chemicals and nutrients. Potential hazardous chemicals include man-made compounds, such as pesticides, food additives and veterinary drugs, as well as naturally occurring substances, such as heavy metals, natural toxins and allergens. In food safety and nutrition, the consumption level of a food or foods and the concentration of a nutrient or hazardous chemical (or mixture thereof) in that food or foods determines the dietary exposure to the chemical and the subsequent beneficial or adverse health effects. These health effects and their likelihood of occurrence in populations are evaluated in a risk assessment: for hazardous compounds the dose needs to be low enough to prevent adverse effects, whereas for nutrients/beneficial ingredients the dose needs to be high enough to achieve the favourable effects while still preventing toxicity from overexposure. Dietary exposure assessment, either external or internal, is an essential step in this process (Fig. 1).

In this paper, the European chapter of the International Society for Exposure Science (ISES Europe) provides a vision on how dietary exposure science can contribute to address the challenges in the field of food safety and nutrition due to changes in food systems by answering the following question: How can we assess timely and accurately changes in dietary exposure to hazardous chemicals (or mixtures thereof) or intake of nutrients due to changes in food production, food consumption and food composition? It must be noted that there are some current challenges that need re-examining, but the focus of this paper is to address the future challenges for dietary exposure assessment sciences.

[1] https://ec.europa.eu/food/safety/chemical-safety/contaminants_en.

2. Current role of dietary exposure science in food safety and nutrition

We shortly address how health risks are assessed in food safety (section 2.1) and nutrition (section 2.2) and how dietary exposure science contributes to this. In section 2.3, we describe the role of human biomonitoring and biomarkers in dietary exposure science. Here, again, we note that there are some current challenges that need re-examining, but the focus of this paper is to address the future challenges for dietary exposure assessment sciences. Some examples of current challenges are:

- Monitoring of chemicals is currently done through regulatory silos, while technically, a lot of analyses could in principle be merged.
- Limit of detections (LODs) should be fit-for-purpose (see later)
- Each EU country is performing monitoring, while this could be more centralized.
- More holistic approaches, such as integrated risk-benefit assessment, could be adapted.

2.1. Food safety

To assess whether there is a risk associated with a hazardous chemical (or group of chemicals) in food, a risk assessment is performed. Such a risk assessment is built on a hazard assessment and dietary exposure assessment. The subsequent phase is to compare the dietary exposure with a safe dose level: risk characterisation. Below hazard assessment and dietary exposure assessment will be further discussed.

2.1.1. Hazard assessment

The first step of a risk assessment is a hazard assessment, which ascertains effects that occur across dose levels and sets the dose (exposure level) that can be ingested without causing adverse health effects. For many chemicals, hazard assessment is based on toxicity studies with rodents and sometimes other animal species. Based on these studies, a Reference Point (RP) - or Point-of-Departure (PoD) - is identified. Examples of RPs are a no-observed adverse effect level (NOAEL), i.e., the highest oral dose showing no effect, or a lower limit of the confidence interval of a benchmark dose (BMDL: benchmark dose lower confidence limit) causing, e.g., a 5% change in effect. By using so-called Uncertainty Factors (UFs) or Safety Factors, the RP is translated into a Health-based Guidance Value (HBGV). Adverse health effects in humans at dietary exposure levels at and below this HBGV are deemed not to occur. UFs cover inter- and intraspecies differences in toxicokinetics and toxicodynamics, but also potential other factors like insufficient duration of exposure in the critical study. In most cases, the applied UF is 100. This derivation of an HBGV can apply to acute effects, resulting in an acute reference dose (ARfD), and chronic effects, resulting in a tolerable daily intake (TDI) for contaminants, or Acceptable Daily Intake (ADI) for intentionally added chemicals. Tolerable Weekly or Monthly Intakes (TWIs or TMIs) are sometimes derived for persistent compounds for which accumulation in the body over time is considered more relevant than an occasionally higher intake.

In the last years, especially for chemical contaminants and when suitable epidemiological studies are available, HBGVs have been identified based on human data. In some of these cases, levels in human specimens (e.g., blood) have been associated with unwanted effects. The use of studies in humans may reduce the uncertainty in risk assessment since interspecies extrapolation is not required.

An important issue in food safety risk assessment is that HBGVs are based on the most critical effect, i.e., typically the one occurring at the lowest dietary exposure level. This critical effect may not always be relevant for the whole population but may only occur in the most sensitive subgroup of the population. For example, for some persistent contaminants like dioxins or per- and polyfluoroalkyl substances (PFASs), HBGVs were derived to protect the unborn child and breastfed

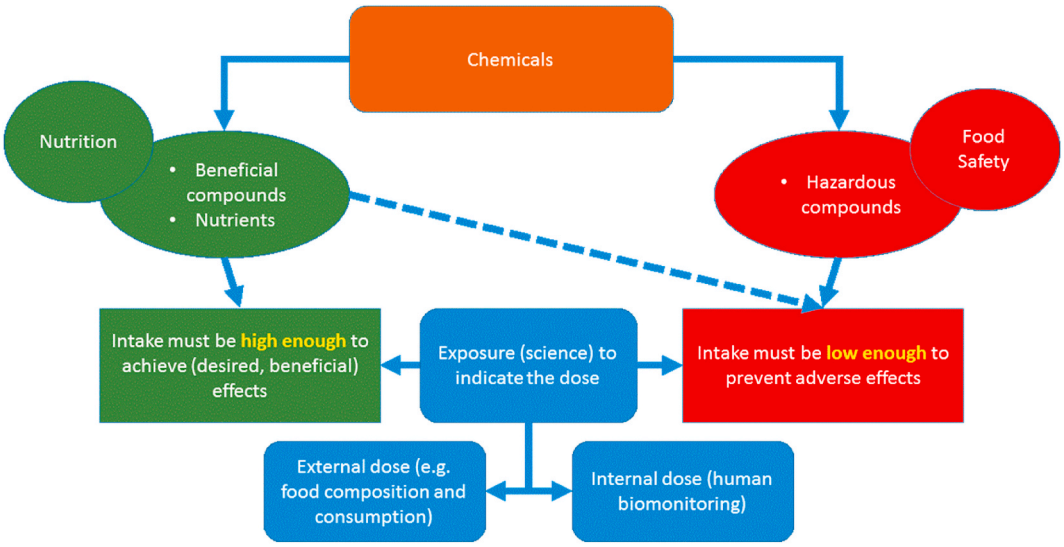

Fig. 1. Interrelationships between food safety, nutrition and dietary exposure science. This graph shows the indispensable role of dietary exposure science in determining the dose that informs the absence and presence of (adverse or beneficial) health effects. Dietary exposure science focuses on external exposure (intake) and/or internal exposure (human biomonitoring). Beneficial compounds/nutrients can also elicit adverse effects at (too) high doses (dotted line).

infant by reducing the dietary exposure of (future) mothers. In general, the idea is that protecting the most sensitive population will also protect the entire population.

Deriving HBGVs as described above is considered not possible for genotoxic carcinogens. For these compounds, no intake level can be derived at and below which no adverse effect can occur. Also in such cases, a BMDL is derived, but this is then used as an RP in the risk characterisation and not for deriving an HBGV. In general, this BMDL is based on the dose causing a 10% increase in the number of animals with tumours, taking into account the uncertainty in the data by establishing a 95% confidence interval (the BMDL is the lower bound of this interval). This $BMDL_{10}$ is compared with a chronic exposure estimate, as assessed by an established methodology or alternative approaches such as Lifetime Average Daily Dose assessments, by calculating a margin of exposure (MOE). An MOE larger than 10,000 by convention is considered to be indicative of "low health concern" (EFSA, 2005). The MOE approach is also applied in the case of contaminants for which the available data on effects are considered insufficient to establish an HBGV. In such cases, an MOE larger than 100 is generally considered to indicate no health concern.

2.1.2. *Dietary exposure assessment*

Dietary exposure assessment combines food consumption data with concentration data of chemicals in food. Assessments may be undertaken for acute or chronic exposure, where acute exposure covers a period of up to 24 h and chronic exposure covers average daily exposure over a longer period, ranging from months up to an entire lifetime. The general equation for both acute and chronic dietary exposure is:

$$Dietary\ exposure = \frac{\sum Concentration\ of\ chemical\ in\ food \times Food\ consumption\ per\ day}{Body\ weight\ (kg)}$$

where:

- dietary exposure = amount of chemical ingested by a person per kilogram body weight per day, for example in µg/kg bw per day;
- concentration of chemical in food = concentration of a chemical in the food consumed, for example in µg/g food;
- food consumption per day = amount of a specific food consumed per day, for example in gram food per day;
- body weight = body weight of the individual consuming the food or the average body weight of a population (subgroup) in kilograms.

When the exposure covers more than one food, the summation is extended to all food items containing the chemical of interest. The term "food" is inclusive of all relevant foods, i.e., solid and liquid foods (including drinking water) and, as far as information is available, food supplements.

Dietary exposure may be calculated using a single consumption and single concentration level, resulting in one single point estimate of exposure (FAO & WHO, 2009). This approach may be taken when only limited information on food consumption and occurrence of the chemical in food is available or to obtain a first high estimate of dietary exposure under conservative assumptions in a stepwise approach. When actual food consumption data at the individual level are available via a food consumption survey, a distribution of consumer chronic exposures can be obtained by multiplying the average daily consumption levels per food of all individuals in the food consumption surveys with the average occurrence level of the chemical in the specific food and adding up the resulting exposures for all foods to arrive at a daily average exposure for an individual. From the distribution of individual average exposures, the mean, the median, and a high percentile (high-level exposure) can be determined, resulting in a dietary exposure estimate that better reflects the chronic exposure in real life. However, food consumption surveys are based on short-term measurements of individual food consumption, typically 2 days, and some bias from within-person variability is present in such chronic exposure estimates resulting in an overestimation of the higher percentiles of exposure (van Klaveren et al., 2012).

More refined dietary exposure estimates can be obtained using a probabilistic methodology, which provides more information on the variability in dietary exposure estimates across the population of interest by including the variation in all input variables in the exposure

assessment. For acute exposure, calculation is done by combining individual daily food consumption levels with randomly drawn levels of a chemical in each food. The exposures per food are added, resulting in an exposure per day for each individual. By repeating this a large number of times, a distribution of daily exposures is generated. By randomly sampling levels from the concentration database, exposure to an incidentally high level in a food product is addressed. Probabilistic approaches also allow the quantification of uncertainty in the input data, by using e.g., the bootstrap approach (EFSA, 2012). For chronic exposure, the probabilistic approach is used in combination with statistical modelling to remove the within-person variability from the exposure estimate resulting in more accurate estimates of higher percentiles of exposure (Boon et al., 2011; Kroes et al., 2002).

Concentration data used to estimate dietary exposure can be obtained from different sources, including total diet studies (TDS) and monitoring data. The essential principles of a TDS are representativeness of the whole diet, pooling of foods, and analysis of food prepared for consumption, e.g. cooked, boiled, fried (EFSA et al., 2011). Whereas TDS are the golden standard for population chronic dietary exposure assessment of ubiquitous chemicals and are broadly applicable to many chemicals (Vin et al., 2014), such studies are carried out in relatively few countries since they are costly, labour-intensive and require harmonization to ensure comparability of results from different countries. In everyday regulatory risk assessment occurrence data originating from monitoring and surveillance programmes are often used to estimate the exposure, because these data are generated regularly due to legal obligations and they are therefore readily available. These data have several limitations. They may not be representative of the concentrations to which people are exposed, because sampling is often targeted at products that are suspected not to comply with legal limits. In addition, monitoring programmes are predominantly focussed on raw products and changes in chemical concentrations due to food processing are normally not taken into account. Furthermore, occurrence data are often available from a limited number of countries, especially for emerging contaminants, and most of the concentration data are produced with analytical methods with poor performance in the context of exposure assessment as they are generated in the frame of compliance testing against regulatory maximum limits. Due to this, a high number of samples may be reported as below the limit of detection (LOD) or limit of quantification (LOQ). Use of these 'left-censored' data in an exposure assessment can result in markedly diverging lower-bound and upper-bound exposure estimates, with the latter often heavily overestimating the actual exposure. In the case of lower-bound exposure, non-detected/non-quantified levels are assumed to be zero, whereas they are set equal to the LOD or LOQ in the case of an upper-bound exposure, as a conservative approach. With these limitations, monitoring and surveillance data are often the only data that are currently available for routinely estimating the dietary exposure to a wide range of chemicals.

Apart from *calculating* dietary exposure, dietary exposure can also be *measured* directly by using the duplicate diet approach. In these studies, subjects collect duplicate portions of all foods they eat during the day and these combined portions are then analysed for the chemical(s) of interest. This design measures actual exposure at the individual level and does not require knowledge of individual food consumption levels and concentrations of chemicals in individual foods. However, these studies are not common, because they are costly and pose a considerable burden on the subject. Due to this, if performed, they usually cover only a limited number of individuals and often one or few days per subject, negatively affecting the representativeness of the dietary exposure results and their use to assess chronic dietary exposure.

2.2. Nutrition

Food is the source of nutrients required for proper growth and health. Nutrients are beneficial compounds as they provide benefits in the form of nutrition. For macronutrients (proteins, carbohydrates, fats, water) and micronutrients (vitamins, minerals, trace elements), several (inter) national bodies have established so-called dietary reference values (DRVs), an umbrella term for a set of nutrient reference values that include the average requirement (AR), the population reference intake (PRI, also called recommended dietary allowance, RDA), the adequate intake (AI), and the reference intake range for macronutrients (RI). It is noted that for nutrition the term 'intake' is used instead of 'exposure'. For an essential micronutrient, the requirement may be defined as the lowest continuing intake level that, for a specified criterion of adequacy, will maintain a defined level of nutriture in an individual. As requirements vary between individuals, there is a distribution of requirements for every micronutrient for any given criterion of adequacy within a population. The AR is the daily intake value that is estimated to meet the requirement in 50% of the individuals in a life stage or gender group. Requirements are usually assumed to be normally distributed and the coefficient of variation (CV) of the requirement is assumed to be 10%–15%. Once the requirement distribution is described, the PRI is the point of the distribution at which the intake is adequate for virtually the whole population group. For most nutrients, assuming a normal distribution, the PRI can be calculated as the AR + 2 standard deviation (SD) of the requirement or, assuming a CV of 10% (15%): RDA = 1.2 (or 1.3) x AR. It should be noted that the DRVs are set in mg (μg)/day and not in mg (μg)/kg bw, as is typically done for HBGVs or BMDLs. Over the past years, EFSA has established a full set of DRVs for micronutrients and macronutrients (EFSA, 2017b, p. 98).

An inherent part of DRV is the Tolerable Upper Intake Level (UL), because nutrients can also elicit detrimental effects at too high levels of intakes (Fig. 1). The UL is an estimate of the highest level of habitual intake that carries no appreciable risk of adverse health effects. Indicators of adverse health effects, which may be used to derive ULs, range from biochemical changes without adverse health effects to irreversible pathological changes in the functioning of the organism. ULs are generally derived for various life stage groups in a population, e.g., adults, pregnant and lactating women, infants, and children. They are derived using the principles of risk assessment as described for food safety (see section 2.1). However, differences exist, notably in the identification of uncertainty factors for deriving the UL from a given reference point. In fact, it must be considered that vitamins and essential elements are subject to homeostatic control whereby the body content is regulated over a range of intakes. Homeostasis reduces the risk of depletion of body pools when intakes are low, but also reduces the risk of excessive accumulation when intakes are high. In practice, the derivation of a UL must consider also nutritional aspects, because it must allow for a sufficient range of intakes above the recommended intake where physiological needs are met and homeostasis occurs so that adverse health effects are prevented in all members of the population. Members of the population with habitual intakes below the UL are at no appreciable risk of adverse health effects, while individuals with intakes above the UL may be at some (unquantified) risk, the magnitude of which depends on the magnitude and duration of the excess.

For macronutrients, the description of too little, adequate and too much applies equally well albeit those requirements are not presented as such but rather as tentative goals, i.e., RIs, expressed as % of the daily energy intake (EFSA, 2017b, p. 98). Intake assessment of nutrients at the population level is typically carried out by combining food consumption data from nationwide surveys with concentration data in food composition tables. TDS provide a much more accurate estimation of nutrient intake at the population level compared to use of food composition tables since the same food consumption data are combined with concentration data from actual analytical measurements of food as consumed (Chen, 2013). If performed regularly over time, TDS can capture changes in, e.g., agricultural practices, food formulation and food processing, and food preparation methods. At the individual level, other approaches, e.g., duplicate diet studies, may be used to assess the intake of nutrients.

2.3. Biomarkers and human biomonitoring

Another way to quantify exposure to compounds present in food can be achieved by human biomonitoring (HBM). In HBM, the levels of the chemical(s) of interest and/or metabolites are determined in human specimens, such as blood, urine, hair or nails. These levels are called biomarkers of exposure. Biomarkers of effect, on the other hand, are measurable biochemical, physiological, and behavioural effects or other measurable alterations within an organism accruing after exposure to chemicals. Depending on the magnitude of exposure, these effects or alterations may be associated with an established or possible health impairment or disease (Zare Jeddi et al., 2021). HBM may be particularly relevant to assess combined exposure from multiple sources - e.g., in addition to food, via medicines, consumer products, the environment (air, soil, dust), or the workplace - and routes (oral, inhalation, and dermal). However, in the case of the general population that is not occupationally exposed, the diet represents the main and, in some cases, almost exclusive source of exposure for most chemicals. As such, the use of HBM can be a complementary approach for dietary exposure assessment (Fig. 1). Examining associations between chemical levels in human matrices and specific biomarkers of effect, chemical levels in, e.g., blood (or plasma/serum), may be derived that are safe for humans. Deriving such levels offers the possibility to evaluate whether the levels observed in the population imply a potential health risk. This is especially the case for persistent compounds where body burden and blood levels build up over time. For less persistent contaminants, blood concentrations will be less informative, because these will depend on the time period between exposure and sample collection. For these contaminants, other matrices like hair or nails may be more suitable. For some compounds (e.g., aflatoxins, acrylamide) metabolism results in the formation of DNA- or protein-adducts.

For the purpose of risk assessment, the 'safe' body burden in humans may be the starting point for deriving a safe intake level, as in the case of dioxins and per- and polyfluoroalkyl substances (PFASs) (EFSA, 2018; 2020a; 2020b). Fig. 2 shows how 'safe' serum levels were used to derive a TWI for PFASs and how this was used in the risk assessment of PFASs in food. A human study on infants was used to derive a critical serum level in infants. Using a physiologically based kinetic (PBK) modelling, this was converted to a critical serum level in the mothers, and a critical intake for the mothers that was the basis for the TWI. Food consumption surveys and concentrations of PFASs in food were used to estimate the exposure which was then compared to the TWI. In addition, data on serum levels in humans were compared with the critical serum levels, confirming that current exposure presents a risk to human health.

So far, interest in HBM has originated mainly from assessing exposure to chemicals from the (working) environment (air/dust, inhalation/dermal exposure), but there is an increasing attention from a food safety perspective (Choi et al., 2015). For example, HBM of many key food contaminants is the basis for the EU project HBM4EU (https://www.hbm4eu.eu/). However, to date EFSA has used HBM data only in a limited number of risk assessments, such as for PFASs (Fig. 2), some other contaminants (lead, methylmercury and dioxins) and for certain pesticides (Choi et al., 2015; EFSA, 2017a).

Human biomonitoring can also be used to estimate the dietary intake of nutrients and has a straightforward interpretation, since nutrients (with few exceptions such as cutaneous synthesis for vitamin D) are taken up via the diet only. Nutritional biomarkers include biomarkers of intake, i.e., indicators of the intake of a given nutrient, and biomarkers of status, i.e., indicators of the nutrient status of individuals/populations. In many cases, nutritional biomarkers are direct indicators of the causal pathway that links the intake of a nutrient to an endpoint or health outcome of interest and, as such, can be used to establish a causal relationship between nutrient intake and a deficiency or excess disease (i.e., establish DRVs). However, for a few nutrients, valid biomarkers have not yet been established. For others, HBM data have been used to set published population reference intakes (PRIs) or adequate intakes (AIs) (Table 1).

Also, the use of biomarkers is a prerequisite in the scientific substantiation of Article 14 Health Claims "… reduction of disease risk claim' means any health claim that states, suggests or implies that the consumption of a food category, a food or one of its constituents significantly reduces a risk factor in the development of a human disease" (Verhagen & van Loveren, 2016).

Finally, specific biomarkers exist which can be used for direct and objective measurement of the intake of specific foods, i.e., to reliably detect food consumption. These are called biomarkers of food intake (BFIs) and are subject of increasing research efforts in recent years (Dragsted et al., 2018). BFIs are a promising tool for limiting misclassification in nutrition research where more subjective dietary exposure assessment instruments are used. They may also be used to assess compliance to dietary guidelines or to a dietary intervention. Whereas, intake markers of many foods can be a valuable instrument in

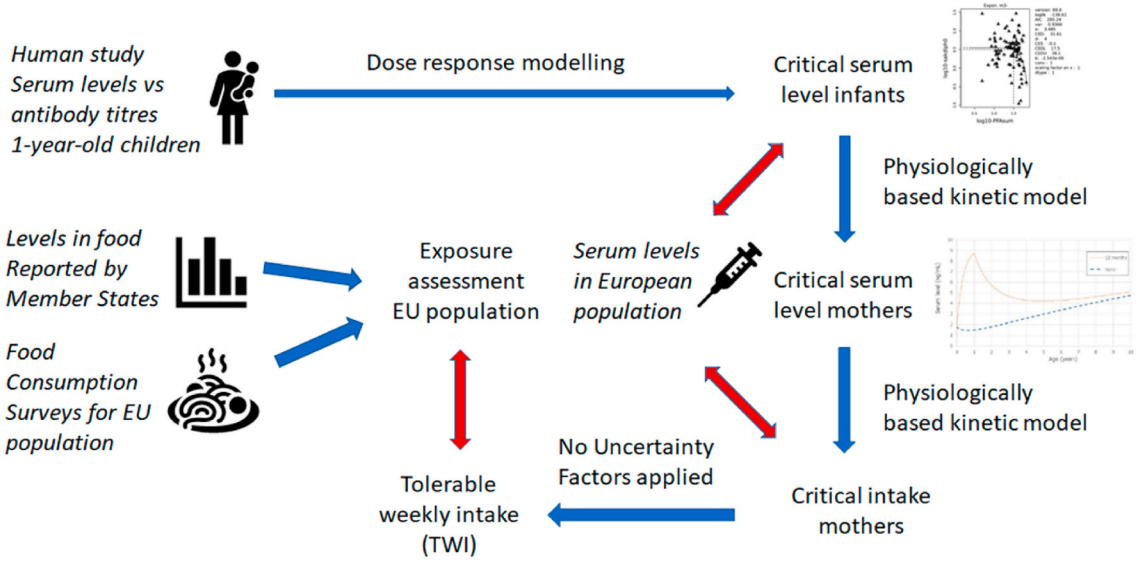

Fig. 2. Risk assessment performed by EFSA on PFASs. This graph shows that serum levels of PFASs, levels of PFASs in food, food consumption information, dose response modelling and a physiologically based kinetic model are needed to estimate the critical serum level and a Tolerable Weekly Intake (TWI) and assessing the risks of PFASs to the European population.

Table 1
Biomarkers used by EFSA for setting the dietary reference values (DRVs) of selected micronutrients.

Micronutrient	DRV	Biomarker	Nature of the biomarker	Reference
Selenium	AI	Plasma selenoprotein P	Biomarker of status	EFSA (2014a)
Folate	PRI	Serum folate/red blood cell folate	Biomarker of intake/ status	EFSA (2014b)
Riboflavin	PRI	Urinary riboflavin (in association to riboflavin intake)	Biomarker of status	EFSA (2017c)
Niacin	PRI	Urinary niacin metabolites	Biomarker of status	EFSA (2014c)
Thiamin (vitamin B1)	PRI	Erythrocyte transketolase activity (in association to urinary thiamin)	Biomarker of status	EFSA (2016d)
Vitamin B6	PRI	Plasma pyridoxal 50-phosphate	Biomarker of status	EFSA (2016a)
Cobalamin (vitamin B12)	AI	Combination of serum cobalamin, holotranscobalamin, methylmalonic acid and plasma total homocysteine	Biomarker of status	EFSA (2015b)
Vitamin C	PRI	Plasma ascorbate	Biomarker of status	EFSA (2013)
Vitamin D	AI	Serum 25(OH)D	Biomarker of status	EFSA (2016b)

DRV: Dietary reference value, AIs: adequate intake, PRI: population reference intake. The reader is referred to the EFSA DRV finder: https://multimedia.efsa.europa.eu/drvs/index.htm for actual numbers.

epidemiological studies on diet-health relationships, at present, the number of comprehensively validated BFIs is limited to just a few (Dragsted et al., 2018). The "food metabolome" approach may provide for a holistic view on food composition and exposure (Scalbert et al., 2014).

3. Current changes and developments relevant for food safety and nutrition

As mentioned in the introduction, the growing world population poses challenges regarding the provision of safe, nutritious and high-quality food. Hereunder, we describe some relevant global and societal developments that provide challenges for dietary exposure science. In section 3.1, we will shortly address the strategies launched by the European Commission (EC) to address these developments. Section 3.2 focuses on the challenges for dietary exposure science of new protein alternatives and section 3.3. on the challenges related to changes in food production. Finally, section 3.4 introduces risk-benefit analysis.

3.1. European strategies on circularity and sustainability

The EC has recently developed the European Green Deal that sets out on making Europe the first climate-neutral continent by 2050. This Deal includes two communications addressing a) Chemicals Strategy for Sustainability; Towards a Toxic-Free Environment (EC, 2020b, p. 667), and b) A Farm to Fork Strategy for a fair, healthy and environment-friendly food system (EC, 2020a). These communications are briefly discussed below, focussing on the elements relevant for dietary exposure sciences.

a) Chemicals Strategy for Sustainability; Towards a Toxic-Free Environment

The European Green Deal aims to improve human health and the environment by tackling pollution from all sources and moving towards a toxic-free environment. The chemical industry is expected to provide safe and sustainable chemicals. It is however recognised that additional exposure routes or new chemicals with hazardous properties may emerge. Already HBM studies in the EU point to a growing number of different hazardous chemicals in human matrices, including pesticides, biocides, heavy metals, plasticisers, PFASs, and flame retardants. Whether this is caused by actual increasing levels or improved detection capability (i.e., lower LODs) is not entirely clear (EC, 2020b, p. 667).

Another important issue regarding chemical exposure is combined exposure to chemicals. In the EU, the safety of chemicals is still mainly assessed through single substance evaluations, without considering the combined exposure to multiple chemicals from different sources and over time (EC, 2020b, p. 667). There is a clear need to adequately address this by integrating combined exposure into chemical risk assessments (EC, 2020a).

The Chemicals Strategy also recognises that a comprehensive, up-to-date knowledge base on chemicals, and their uses and exposure, is needed for robust decision-making. Assessing the presence of chemicals in humans and ecosystems is key to improve the understanding of their impact, and should be further promoted (EC, 2020b, p. 667).

b) The Farm to Fork Strategy for fair, healthy and environment-friendly food systems

The Farm to Fork Strategy addresses the challenges of sustainable food systems, and recognises the links between healthy people, healthy societies and a healthy planet. For this, food production, food processing, and food consumption should become more sustainable, including reduction of food loss and waste (EC, 2020a). Environmental sustainability is a key element in the light of the indissoluble interrelationship linking human health, animal health, and the environment, which is at the base of the One Health concept (WHO, 2021). Chemical food contamination is a major cross-cutting issue for many chemicals, including antimicrobials, used in animal and plant production. Therefore, One Health monitoring and surveillance systems clearly include chemical hazards (WHO, 2021).

3.2. Changes in food consumption or food composition

Changes in food consumption or food composition also pose challenges for dietary exposure science. Important drivers of these changes are the scarcity of sources, health trends and the growing need for non-animal products, for example because of animal welfare or sustainability reasons. Due to this, there is an increasing demand for protein alternatives (Westhoek et al., 2011). These alternatives vary from an entire plant-based or vegan diet to mixtures of diets composed of animal and plant proteins (van der Weele et al., 2019). Among animal proteins, fish and seafood feature prominently as healthier and more sustainable protein sources compared to meat. They are naturally rich in valuable nutrients, including n-3 long-chain polyunsaturated fatty acids with well-established health benefits, and are components of dietary patterns associated with good health (EFSA, 2014d). However, fish/seafood can also contain hazardous compounds such as methylmercury, dioxins, PCBs and PFASs. As such "fish" is the most widely studied example among risk-benefit assessments (RBAs) in food safety and nutrition (Thomsen et al., 2021). There is potential for a more sustainable fish and seafood production entailing reduction of wild fish capture (i.e., bringing fish stocks to sustainable levels) and diversification of the species (with increased use of underutilised nutrient-rich small fish). In addition, a further growth of aquaculture would generate a lower carbon footprint than animal production on land. Furthermore, with innovative solutions, such as Integrated Multi Trophic Aquaculture, improved feed formulation and production can be pursued (e.g., see seafoodtomorrow.eu). These changes in seafood species and/or production processes may have a positive or detrimental impact on the dietary exposure to environmental contaminants (e.g., methylmercury, dioxins, PCBs and

Box 1
Food safety issues of seaweed

Background

Seaweeds are used extensively as food in coastal cuisines around the world. For example, they have been a part of diets in Asian countries since hundreds of years. Seaweeds are also harvested or cultivated for commercial uses for the extraction of polysaccharides such as alginate, agar and carrageenan, gelatinous substances collectively known as hydrocolloids or phycocolloids (García-Vaquero et al., 2017). Seaweed oil is used as a source of fatty acid dietary supplement, as it contains mono- and polyunsaturated fats, as well as for biofuel, massage oil, soaps, and lotions (Doughman et al., 2007). Seaweed is becoming more and more popular in Western countries, as a source of phycocolloids used as food additives or as an alternative to animal protein. As such it presents an interesting case in relation to exposure to various nutrients and contaminants.

Other than the legislative question whether or not some particular species of seaweed in Europe should be dealt with under Regulation (EU) 2015/2283 on Novel Foods, seaweed also comes with food safety issues. Seaweed testing for contaminants can show high levels of heavy metals (cadmium, mercury), arsenic, and iodine (Banach et al., 2020), although these levels vary between species and collection sites (Roleda et al., 2019). As regards to iodine, being a nutrient, an adequate intake is necessary, while an excess intake can lead to adverse effects, primarily disturbed thyroid functioning (ATSDR, 2004; EC, 2002). The German Institute for Risk Assessment advised that dried algal products containing an iodine content greater than 20 mg/kg should not be placed on the market, assuming a daily intake of 10 g of dried seaweed, as they could harm health (BFR, 2007). Recently, a risk-benefit assessment was made of replacing several items of the diet with seaweed, which found that an increased seaweed consumption has no consequences in terms of intake of sodium, and exposure to cadmium, lead and mercury and the associated (absence of) adverse health aspects. In contrast, the seaweed scenario almost doubled the mean iodine intake and increased the average exposure to arsenic levels, the public health consequences thereof may trigger further research (Vellinga et al., 2021-Accepted).Another key contaminant is inorganic arsenic, the most toxic arsenic form, for which exposure should be reduced (EFSA, 2009, 2021e). Assessment of seaweed safety with respect to arsenic is challenged by the need to have information on the type of arsenic species present (Cubadda et al., 2017). Whereas total arsenic is uniformly high in seaweed because of the high content of organic arsenic species, high inorganic arsenic concentrations are notable in a few species. As for iodine, they seem to be also affected by factors such as sampling location, depth of cultivation, and seasonal variability (Banach et al., 2020). Therefore, in the case of seaweed, the capability to discriminate organic and inorganic arsenic is crucial. The significance of arsenic speciation in exposure assessment is addressed further below.

Exposure issues seaweed

As the production and consumption of seaweed or seaweed products increase, the following exposure related food safety knowledge gaps can be discerned (based on (Banach et al., 2020)):

- the location of seaweed cultivation, which may affect the contamination, and its relation to optimal growth conditions, e.g., sufficient nitrogen availability;
- the effect of processing and cooking of seaweed on levels of iodine and contaminants;
- more information on levels of iodine and contaminants, and e.g., more specifically on the organic and inorganic species of arsenic. Additional concerns include the presence of marine biotoxins, phytotoxins, or allergens from other marine-based products grown near seaweed or other compounds occurring naturally in seaweed, and the levels of all these chemicals in different species of seaweed;
- more information on consumption of different types of seaweed;
- more information on the effects of e.g., iodine in populations that regularly consume seaweed.

PFASs) in seafood.

A new and emerging plant protein source is seaweed, very common in Asian countries, and becoming more popular in the Western world. Some seaweed species can contain high levels of iodine, bromine and heavy metals (see Box 1). Other protein alternatives are microalgae and duckweed, which add to more traditional (but still key) protein sources such as legumes. In the animal protein domain, in addition to fish and seafood, breeding insects has grown intensively during the last decades. Insects can also be reared on organic residual and waste streams (Oonincx & De Boer, 2012), turning waste into useful feed for farm animals (Rumpold & Schlüter, 2013a; 2013b). It is expected that this use of insects as a protein source will increase since European legislation has recently opened the legal door for permitting insects as a feed source for fish farms. Lately, insect species have also been positively assessed for safety in view of their use in the EU as human food (EFSA, 2021g, 2021i). Lastly, artificial meat as an alternative to animal proteins is still a novelty but may also grow as an alternative source of protein (Bonny et al., 2017). Moreover, digital innovation and transformation, for example, genomics and related tools are trends that are rapidly changing food systems (WHO, 2021).

These new or emerging protein alternatives may present potential health issues. Insects may, for example, accumulate heavy metals from breeding on waste (van der Fels-Klerx et al., 2018) or may contain antinutrients that are usually present in plant materials but that many phytophagous insects have been identified to retain in high quantity (BuRO, 2019; Meyer-Rochow et al., 2021). Food safety thus needs further attention as these alternatives further emerge, especially the appraisal of contaminant levels and consumption levels, which are the area of dietary exposure science. In Europe, these new protein sources need to undergo a submission process at part of the 'Novel Food' regulation (Regulation (EU) 2015/2283) (EFSA, 2021f), which demands a safety assessment prior to marketing. For this, information is needed on the food composition and nutritional value, the levels of possible chemical and microbial contaminants, the consumption of these proteins, as well as the toxicological properties and the potential allergenicity of the proteins; in specific cases a dietary exposure assessment is carried out based on the expected use and consumption levels (Ververis et al., 2020).

3.3. Food-production related issues

In this section, we will describe, by using some specific examples, several global developments related to food production that pose a challenge for dietary exposure science.

3.3.1. Food packaging materials

As part of more sustainable food production, there is an increasing use of recycled products in food packaging, which may result in more hazardous chemicals present in food packaging materials. For example, paper and cardboard already contain more than 8000 chemicals, the

great majority for which no toxicological information and no information on migration from the packaging material to food is available (Van Bossuyt et al., 2016). Furthermore, annually over 400,000 tons of printing ink is used in the EU for labelling and printing of food contact materials (FCMs) (Simoneau et al., 2016, p. 28357), for which also very little toxicological information is available nor knowledge on migration of chemicals from the ink into the food. For these reasons, a better safety assessment and a stricter control of FCMs is needed. The current EU Regulation 1935/2004 sets out that FCMs should not emit chemicals that can harm human health, change the food composition in an unacceptable manner or negatively affect organoleptic properties of the food. This regulation is, however, not very effective in assuring food safety, and the upcoming revision of the EU legislation of FCMs is needed to address this increased use of recycled products in food packaging (Van Bossuyt et al., 2016).

Most likely, the need for dietary exposure assessment for FCMs will be a major element of future legislation. The migration of hazardous chemicals from FCMs and ink into food depends on the properties of the FCM and ink, the composition of the food, and storage time and conditions (Barnes et al., 2006). These hazardous chemicals can be individual chemicals or mixtures of Intentionally Added Substances (IAS) and Non-Intentionally Added Substances (NIAS).

3.3.2. *Reducing organic waste*

To reduce waste, the bio-based economy is an important phenomenon. The bio-based economy (Sanders & Langeveld, 2020) aims at reducing organic waste by making better use of plant parts that were earlier discarded, but are now used to produce biofuel and bio-products, such as bio-based FCMs. For example, there are already plastic spoons of biobased origin on the market and cups made of resin and bamboo material. Migration of formaldehyde and melamine from this resin and bamboo material has been shown to occur, even throughout the service life (Mannoni et al., 2017), indicating that these new bio-based FCMs require consideration from the standpoint of food safety in order to assess if dietary exposures to chemicals from these materials may pose risks.

3.3.3. *Climate change*

Changes in climate may affect the levels of natural contaminants in food products, such as mycotoxins (Miraglia et al., 2009). Mycotoxins are produced by certain moulds that require specific conditions for optimal growth. For example, there was an incident with aflatoxin contamination of maize in Serbia due to climate change in 2013 (De Rijk et al., 2015).

Climate change may also promote the growth of certain weeds that produce plant toxins that may end up in food products. Thus far little information is available on these aspects. Furthermore, it should be stressed that also changes in the use of agrochemicals, such as fungicides, pesticides or herbicides, may influence the levels of plant toxins and mycotoxins in food. A shift in production locations with different climatic conditions may be relevant as well.

In addition, climate change poses enormous threats to food adequacy (i.e. food security) and nutrition at the global and regional level (Miraglia et al., 2009). It may affect access to essential amino acids and drives the current focus on alternative sources of protein (insects, algae, cultured meat, legumes, etc.). If intake of essential amino acids is too low, it will have consequences for the nutritional state and public health (Westhoek et al., 2011). Likewise, adequate provision of several micronutrients, such as vitamin A, vitamin D, iodine, iron, zinc, folic acid are of relevance for public health (EFSA, 2017b, p. 98).

According to the FAO (FAO, 2020), "as our world and food systems adapt to climate change, food safety authorities everywhere must be cognizant of the issues on the horizon to prepare for upcoming challenges. Intelligence gathering and foresight are useful tools that can be used to adopt a preventive perspective to food safety and nutrition as opposed to a reactionary approach. Alongside intelligence techniques, these tools will help countries to avert hazards and keep food available and safe".

3.3.4. *Shifting to more animal-friendly housing*

The tendency to let animals forage outside, for example for reasons of improving animal welfare, implies that contaminant levels in pastures and courtyards become more relevant as certain chemicals may accumulate in tissues or transfer to edible products like milk, meat and eggs (Schoeters & Hoogenboom, 2006).

3.3.5. *Nanotechnology*

Applications of nanotechnology in agricultural production, food processing, and FCMs are rapidly developing (Rossi et al., 2014). Nanotechnology applications in the food sector may bring benefits, but also risks. Potential risks have to be assessed using tailored risk assessment approaches (EFSA, 2021d). Relevant information for performing an appropriate nano-specific risk assessment is also required for a number of currently used food additives and nutrient sources in particulate form, which are not nanotechnology products but present properties that are characteristic of the nanoscale (EFSA, 2021a; Schoonjans et al., 2021).

All this poses exceptional challenges to dietary exposure science, since identification of the agent entails a physico-chemical measurement (including the determination of particle size and other properties) instead of the detection of a simple (soluble) chemical. Furthermore, nanomaterials may agglomerate/aggregate and form bigger particles or disintegrate and form smaller particles depending on the matrix they are in. If nanomaterials are used in agriculture, it has to be assessed if they reach the final consumer via carry-over. If they are used in FCMs, actual particulate release from food packaging has to be assessed. On the other hand, if they are intentionally added to food (e.g., as nutrient sources, which qualify the source as a Novel Food under Regulation (EU) 2015/2283), their presence as particles should be assessed at the moment of consumption (non-particulate degradation products would be assessed via 'conventional' risk assessment). Finally, and most importantly, nano-specific risk assessment is required only if the particles reach the human intestine as such in a way that local or systemic exposure may take place: however, an exposure assessment to agents of particulate nature implies significant technical issues.

3.4. *Risk-benefit assessment*

Food provides nutrition and is assumed to be safe if correctly handled. However, foods that contain necessary and beneficial ingredients, may also contain chemicals with potential adverse effects. For example, fish contains healthy n-3 fatty acids, but can also contain methyl-mercury, dioxins and PFASs (Thomsen et al., 2021). To address this, an RBA may be performed.

RBA is relatively new in the area of food safety and nutrition. In assessing the various health effects associated with food consumption it is important to take into account the opposing starting points related to risks and benefits (Verhagen et al., 2021). Risk assessment for food safety is typically based on dose levels without an effect derived from either animal toxicity studies or human epidemiological studies (see section 2.1). Benefit assessment for nutrition is typically based on dose levels with clear (beneficial) effects (see section 2.2). RBA envisages expressing both risks and benefits of foods and food ingredients by comparable measures or units, thereby allowing for a quantitative comparison of health impact assessments of adverse and beneficial effects (Boobis et al., 2013; Boué et al., 2015; EFSA, 2010; Membré et al., 2020; Tijhuis et al., 2012; Verhagen et al., 2012). In addition to RBAs also further related approaches exist, such as cost-benefit assessment, Burden-of-Disease calculations, and risk ranking.

In Box 2 the main challenges for dietary exposure science are summarised as extracted from the current changes and developments relevant for food.

Box 2
Main challenges for dietary exposure sciences

- Chemicals Strategy for Sustainability; Towards a Toxic-Free Environment
  - o Increased likelihood that dangerous chemicals will occur in food contact materials or in the food chain
    - oThe increasing political wish to show that food is 'toxic-free'
    - oIncreasing need for analytical studies of food and food contact materials
    - oIncreasing need for human biomonitoring studies to capture the level of exposure and to measure the effectiveness of regulations on chemical contaminants in food to ensure a high level of human health protection
    - oIncreased need to protect consumers, particularly the vulnerable populations (e.g., pregnant women, children etc.) from being exposed to chemicals that cause cancers, gene mutations, affect the reproductive or the endocrine system, and/or are persistent and bioaccumulate
    - oIncreasing need to safeguard consumers from toxicity as a result from exposure to combined exposure to multiple chemicals (mixtures), and the need for methods to assess exposure and risks
    - oThe overall need to improve knowledge on use patterns, exposure routes and pathways to chemicals
    - oExtend the principle of open data and the relevant transparency principles from the food safety sector to other pieces of chemical legislation
- A Farm to Fork Strategy for a fair, healthy and environment-friendly food system
  - oMonitor the reduction of use of pesticides
  - oMonitor how feed additives can reduce the impact of livestock farming
  - oSetting maximum levels for certain nutrients following the restriction of food high in salt, sugars and/or saturated fat
- WHO global strategy for food safety 2022–2030
  - oStrengthening national food controls
  - oIdentifying and responding to food safety challenges resulting from global changes and transformations in food systems
  - oIncreasing the use of food chain information, scientific evidence, and risk assessment in making risk management decisions
  - oPromoting food safety as an essential component in domestic and international food trade
- Changes in diet or food composition:
  - oThe need to assess the consumption of novel foods (EFSA, 2021f) and the dietary exposure to additives
  - oMonitor the chemical quality of novel foods and additives, and the effect of culturing or producing those on chemical quality
  - oMonitor the nutrient level of novel foods and additives, and the effect of culturing or producing those on nutrient level
- Food contact materials (FCMs):
  - oThe presence of (mixtures of) Intentionally Added Substances (IAS) and of Non-Intentionally Added Substances (NIAS) in FCMs and their migration to food that might have hazardous properties
- Reducing waste
  - oThe presence of (mixtures of) chemicals, of natural origin or not, in biobased FCMs
  - oPlastic waste in the form of nano and microplastics
- Avoiding food spillage
  - oMonitoring the chemical quality and nutrient levels of food otherwise spilled
- Climate change
  - oThe presence of mycotoxins in food (products)
  - oThe presence of plant toxins in food (products)
- Animal welfare
  - oContaminant levels in pastures and courtyards
- Nanotechnology
  - oThe presence of particulate agents in food and their physical-chemical characterization
  - oThe persistence of particles as such (i.e., non-degradation or dissolution to 'conventional' soluble chemicals) in the human intestine after gastro-intestinal digestion
- Risk-benefit assessment
  - oHolistic approaches in risk assessment: risk-benefit assessment, cost-benefit assessment, Burden-of-Disease calculations, risk ranking

4. Dietary exposure sciences in food safety and nutrition: future perspectives

As explained and illustrated in chapter 3, food safety and nutrition face various challenges. Below we will address some future perspectives on how dietary exposure sciences can contribute to tackling these challenges.

4.1. Chemical analysis

To address some of the challenges, a stronger focus is needed on a) limits of detection (LOD) and limits of quantification (LOQ) in chemical analysis, and b) the scope of the methods. Ideally, LODs/LOQs should be low enough that when all concentrations are below these limits, the outcome of a risk assessment based on an upper-bound scenario would show a negligible risk. For well-known contaminants with well-established hazard characteristics, the required LODs/LOQs in the various food matrices are known and available methods are often, but not always, sensitive enough. These methods, however, are often directed to a very specific group or even a single chemical (e.g., dioxins or aflatoxin M1). Hence a multitude of methods is needed to cover the many chemicals that might occur as single chemical or as mixtures in our food. To improve throughput and reduce costs, multi-analyte/multi-matrix analysis methods are needed. While the possibilities for this have substantially improved in the past decade, due to more efficient sample preparation approaches and availability of more sensitive and selective instrumentation (LC-MS/MS, e.g., (Hird et al., 2014), GC-MS/MS, e.g., (Kalachova et al., 2013), ICP-MS, e.g. (Patriarca et al., 2021)), the implementation and application in monitoring laboratories is still lagging behind (Lehotay & Chen, 2018). In the area of trace elements, the capability to distinguish species with markedly different biological and toxicological properties (e.g., by LC-ICP-MS (Lorenc et al., 2020)) is still largely limited to expert laboratories whereas in these cases speciation analysis is key for both risk assessment and risk management.

Apart from the need for analytical methods to provide better and more data on the commonly known chemicals, there is also the need to

cover emerging chemicals present in our food. Wherever possible, the known emerging chemicals should be incorporated in (multi-analyte/multi-matrix) analysis methods used in monitoring programmes to simultaneously generate data on the classical and the emerging chemicals. More challenging is the detection of chemicals that are not known or not expected to occur in food, not known to be hazardous, or even unknown to exist. For this, new analytical approaches are needed. A non-targeted measurement based on chromatography with full scan high resolution mass spectrometry (LC-HRMS, GC-HRMS) is a very promising option for this (Fu et al., 2017; Shao et al., 2019). A main challenge here is how to identify 1000s of known or even unknown chemicals in the very complex data from this type of measurement (Knolhoff & Croley, 2016; Kunzelmann et al., 2018; Milman & Zhurkovich, 2017). More research is needed on this before it can be implemented in monitoring programmes.

Another option is the use of bioanalytical techniques where bioassays are used to detect all compounds with a specific effect, e.g., binding to the arylhydrocarbon, estrogen or androgen receptor. Various assays are available and sensitive enough to be applied in routine monitoring as a screening assay. Samples with an elevated response can then be examined for known contaminants or unknown in case the bioassay response cannot be explained.

For analysis in the frame of HBM, the needs and perspectives are in general similar as indicated above for food. HBM data can complement the food analyses and enable linking external dietary exposure to internal exposure. However, for many chemicals, methods for identifying the relevant exposure and effect biomarkers still need to be developed (Zare Jeddi et al., 2021). Compared to food, the number of matrices is limited for assessing exposure biomarkers (mainly urine and blood) via HBM. On the other hand, especially for urine, the target analytes are often metabolites of the chemicals and the availability of analytical reference standards, needed for identification and quantification, can be challenging. Also, non-targeted approaches are highly promising in HBM (Pourchet et al., 2020), although the same limitations regarding data handling as described above for food need to be addressed here.

An area with considerable analytical challenges is micro- and nanoplastics (EFSA, 2016c). These plastics are emerging contaminants in food chains and - similarly to engineered nanoparticles - have both a physical (particle shape, size and size distribution) and a chemical (composition, i.e., polymer nature) dimension. Plastic waste in the form of nano and microplastics has the potential to enter/re-enter the food chain from aquatic, soil and atmospheric sources. There are currently no reliable exposure estimates for these contaminants. They require occurrence data based on well-defined and comparable ranges for the particle size, either in the micro- or the nano-size range, and a thorough chemical characterization (EFSA, 2021c). Currently, a reasonable approach to address this challenge appears to be the development of multi-technique analytical protocols entailing analyte extraction and preconcentration (especially for the nanoplastics), separation of the plastic particles into specific size fractions, size characterization of the particle fractions by means of light scattering techniques and electron microscopy, and chemical identification of constituting polymers (Schwaferts et al., 2019).

4.2. Food composition

To assess the effect of changes in food composition (for example increased consumption of foods containing protein alternatives) on food safety and nutrition requires insight in the nutritional composition and the presence of toxicologically relevant chemicals in these new foods. In addition, the bio-based economy will result in new bio-based food contact or packaging materials, such as spoons and cups. Improved analytical techniques are needed to reveal the effects of these novel trends. Depending on the goal of the assessment and the level of protection needed, assessments deal either with the whole population or consumers only and this will also depend on the number of foods that could contain the chemical. Regarding the new foods, information is needed on how many people will consume these foods, how frequently and in which amounts, and whether these foods are processed at an industrial scale or cooked at home (raw, cooked or baked). This information needs to be captured in national food consumption surveys or, if only consumed by a specific part of the population, by conducting dietary studies targeted at these populations.

4.3. Dietary exposure and human biomonitoring

Assessing the dietary exposure to hazardous chemicals and the intake of nutrients requires information on both food consumption and chemical concentrations in food. Concentration data for hazardous chemicals may originate from TDS or monitoring and surveillance programmes, which should be adapted to the changes in food production methods and changing food consumption patterns. For nutrients, concentrations are commonly derived from food composition tables, but these need to be more frequently and effectively updated to reflect changes in dietary patterns. For all changes in diet, dietary exposure science should be based on food consumption data for the general population or subgroups that may be more highly exposed due to their vulnerability or consumption habits.

Approaches to more accurately estimate population dietary exposure, such as generating chemical concentration data using TDS and/or performing refined probabilistic distributional analyses to capture the variability and uncertainty in dietary exposure, are needed to address the current and future changes in diet and food composition. If feasible, dietary exposure assessment should be more comprehensively complemented with HBM techniques, reflecting the aggregated exposure of the individual from different sources or through different exposure routes. In order to translate a 'safe' body burden (i.e., levels in tissues or blood not associated with an effect) in humans into a safe external exposure level, toxicokinetic models are suitable tools, as shown for dioxins and PFASs (see section 2.3). These models should be further improved and extended to other classes of chemicals. All these approaches should cover both exposure to single chemicals and mixtures of chemicals.

4.4. Nutrients

Intake of nutrients is related to the nutritional composition of foods. This is of relevance for scientists and also for consumers. As concerns the latter, to better inform the consumer on nutritional values of food, a harmonised mandatory front-of-pack nutrition labelling is foreseen. Nutrient profiles or logos based on nutrient profiles can help to restrict promotion of food that is high in salt, sugar and/or fat (Van Der Bend et al., 2014) (Verhagen & van den Berg, 2008). Alongside nutrient profiles, DRVs are pivotal for informing nutrition policies. As such, policies and management options are based on the availability of updated DRVs, reflecting current scientific evidence. Whereas this is the case for PRIs/AIs, the setting of most ULs dates back to more than 20 years ago. ULs of several micronutrients, for which the risk of overexposure and associated adverse health effects is concrete, need to be reassessed. The identification of appropriate biomarkers of intake and biomarkers of effect, useful for the characterization of dose-response relationships at intakes above the adequate range of oral intake, is pivotal for such reassessment. This is undoubtedly a challenge that dietary exposure science in the nutritional domain will have to address.

A more thorough use of HBM to assess the nutrient intake and status of individuals is also foreseen. Whereas a one-size-fits-all approach may fail, personalized nutrition can empower consumers to adhere to a long-lasting, healthy, pleasurable, nutritional and sustainable diet when tailored to individual parameters such as the physical and psychological characteristics (health status, phenotype, genotype, microbiome configuration, food metabolome, etc.), the needs and preferences, behaviour, lifestyle, and budget; alongside to general economic factors

(e.g., market prices) and socio-cultural aspects. The use of appropriate biomarkers may allow to monitor the effectiveness of personalized nutrition in ensuring an optimal nutrient status of individuals for warranting optimal health and with the long-term goal of the prevention of diet-related chronic diseases. Whereas a healthy diet is sufficient and balanced in terms of quantity, quality and safety (WHO/FAO, 2019), currently a large proportion of the world population is malnourished and the impact thereof is responsible for about 11 million diet-related preventable deaths globally per year (Gakidou et al., 2017; Stanaway et al., 2019).

4.5. Risk-benefit assessment

As explained in section 3, an RBA may be relevant for foods or food groups containing both beneficial and hazardous chemicals, such as fish. RBA is best performed as part of a tiered approach, comparing at least two scenarios (Boobis et al., 2013; Boué et al., 2015; Nauta et al., 2018; Tijhuis et al., 2012; Verhagen et al., 2021), and stop once enough information is available to weigh the risk and benefit of eating a food. When taking an RBA further, there are ample opportunities and challenges. The developments in science in the area of food safety risk assessment merit attention, such as the EFSA-led topics Uncertainty, Weight-of-Evidence, Biological Relevance, and the Prometheus approach (EFSA, 2015a). All these developments can contribute to refine scientific RBAs and can then inform evidence-based risk-benefit management.

5. Conclusions

Overall, food production, food consumption and food composition are changing as a result of global developments. These changes will affect the dietary exposure to hazardous chemicals and intake of nutrients, either for good and/or for bad such as an increased exposure to mycotoxins, nanoplastics, endocrine active substances and an altered supply of essential amino acids and micronutrients. In addition, also other changes such as improved analytical techniques allowing us to measure chemicals at much lower levels will affect insight in dietary exposure and intake, and increase knowledge about the effect of exposure to mixtures of compounds on consumer's health. In this paper, we focussed on how dietary exposure science can contribute to the timely and accurate assessment of the impact of these changes on consumer's health. For this, several developments were discussed that require special attention to improve and ascertain public health in relation to the exposure to hazardous chemicals and intake of nutrients. These include:

- Improving chemical and bioanalytical techniques to accurately quantify levels of contaminants in food, to detect and identify emerging chemicals and to assess the presence of mixtures of chemicals.
- Identifying potential impacts of new technologies such as nanotechnology on the flows of (particulate) chemicals to agricultural/food systems.
- Studying the potential impacts of changes in food systems (food production, food composition and food consumption) on human exposure to chemicals and nutrients.
- Taking advantage of modern approaches such as HBM, TDS and RBA to improve dietary exposure and risk assessment.

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Maryam Zare Jeddi: Conceptualization, Writing - Original Draft. Polly E. Boon: Writing - Review & Editing. Francesco Cubadda: Writing - Review & Editing, Ron Hoogenboom: Writing - Review & Editing. Hans Mol: Writing - Review & Editing. Hans Verhagen: Visualization, Writing-Reviewing and Editing, Dick T.H.M. Sijm: Supervision, Writing - Review & Editing.

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