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Review

Current and emerging issues in chemical food safety

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Liang Zheng²



Food safety is increasingly influenced by global challenges, such as climate change, environmental pollution, the shift toward plant-based diets, and new technological developments. This review addresses key issues currently shaping chemical food safety, focusing on natural toxins in plant-based foods, the effects of climate change on food safety, and the role of endogenous compound formation in exposure assessments. The review also discusses the growing concern over per- and polyfluoroalkyl substances and nanomaterials and examines advances in risk assessment, particularly the adoption of new approach methodologies (NAMs) and the integration of innovative technologies such as artificial intelligence. These topics underscore the need for updated risk assessment practices and offer insights into how food safety standards and regulations might evolve in response to these emerging challenges.

Addresses

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Introduction

The increasing human world population, global warming, environmental pollution, and new technological developments as well as new scientific insights bring challenges and newly emerging issues to the field of food safety. The current review presents some of these current and emerging issues, including (i) natural

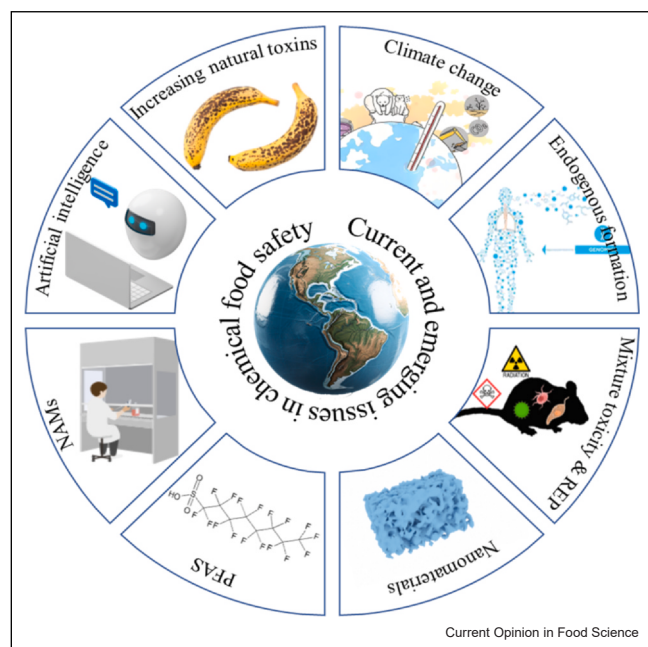
toxins accompanying the use of more plant-based foods to increase the sustainability of our food chain and food security, (ii) effects of climate change, (iii) the role of endogenous formation for the exposome and risk assessment, (iv) effects of mixtures and the importance of relative potencies, (v) nanomaterials and per- and polyfluoroalkyl substances (PFAS), (vi) novel food packaging, and (vii) the use of new approach methodologies (NAMs) and artificial intelligence (AI) in risk assessment (Figure 1).

For each of these topics, the current and future perspectives are presented with a focus on impacts on food safety. It is concluded that in a changing world and climate and based on new insights, hazard risks related to the modern food chain and the assessment of their consequences for food safety are changing as well.

Natural toxins accompanying the use of more plant-based foods

The increasing number of people and accompanying demands for food and feed pose an imminent threat to global food security, the environment, and biodiversity and have resulted in a significant growth of the plant-based food market [1]. Plant-derived foods, including grains, fruits, vegetables, legumes, and nuts, become increasingly important in the human diet, and new plant-based foods mimicking meat, seafood, or dairy are often prepared from plants [1]. These plant-based foods may come with new food safety issues to be considered. Plant-based raw materials and foods derived from them may contain natural toxins, and mimicking the sensory characteristics of meat, seafood, or milk may require substantial processing and manipulation. Consumers may even avoid such products because they are considered 'too processed' and with 'too many preservatives' [2]. The levels of natural toxins in plant-based foods may vary depending on growth conditions or location, plant variety, and processing or storage conditions. Improper food handling, for example, may be the cause of exposure to toxic levels of natural toxins, such as antinutrients, glycoalkaloids, quinolizidine alkaloids, cyanogenic glycosides, or mycotoxins like aflatoxins and deoxynivalenol [3]. Additionally, dietary trends like raw foodism may increase toxin exposure. Cooking traditionally helps to inactivate toxins like lectins or cyanogenic glycosides, but raw food consumption bypasses these protective steps, resulting in potential toxicities that were otherwise mitigated. Furthermore, some plant

Figure 1



Current and emerging issues in chemical food safety.

toxins, such as allylalkoxybenzenes and pyrrolizidine alkaloids (PAs), naturally present in some botanicals, may result in intakes at levels that raise a food safety concern [3]. In addition, switching varieties, for example, by accident, in situations of shortage of a raw commodity or in cases of food fraud in a competing market, may introduce food safety issues such as in the case of the neurotoxin anisatin present in Japanese star anise (*Illicium anisatum*) used to replace the Chinese variety (*I. verum*), which does not contain this toxin or the unintentional exposure of young women to aristolochic acids via a herbal weight-loss preparation in which *Stephania tetrandra* was mistakenly replaced by *Aristolochia fangchi* causing kidney damage developing into cancer of the kidneys [3]. Additionally, plant-based foods like tree nuts, peanuts, soybean, and wheat may bring a risk of allergenicity especially to sensitive individuals.

Taken together, it is clear that our modern food chain contains toxins from raw plant-based material so the increased use of plant-based raw material may increase the accompanying food safety issues.

Effects of climate change

Climate change impacts weather patterns, often increasing temperatures and posing threats to food safety through mechanisms such as heightened foodborne disease risks and elevated levels of chemical hazards, including pesticide residues, mycotoxins, and heavy metals [4,5]. These impacts are particularly significant

for plant-based raw materials, as the level of natural toxins present in these materials and the foods derived from them depends heavily on environmental conditions such as climate, soil, watering, and storage conditions.

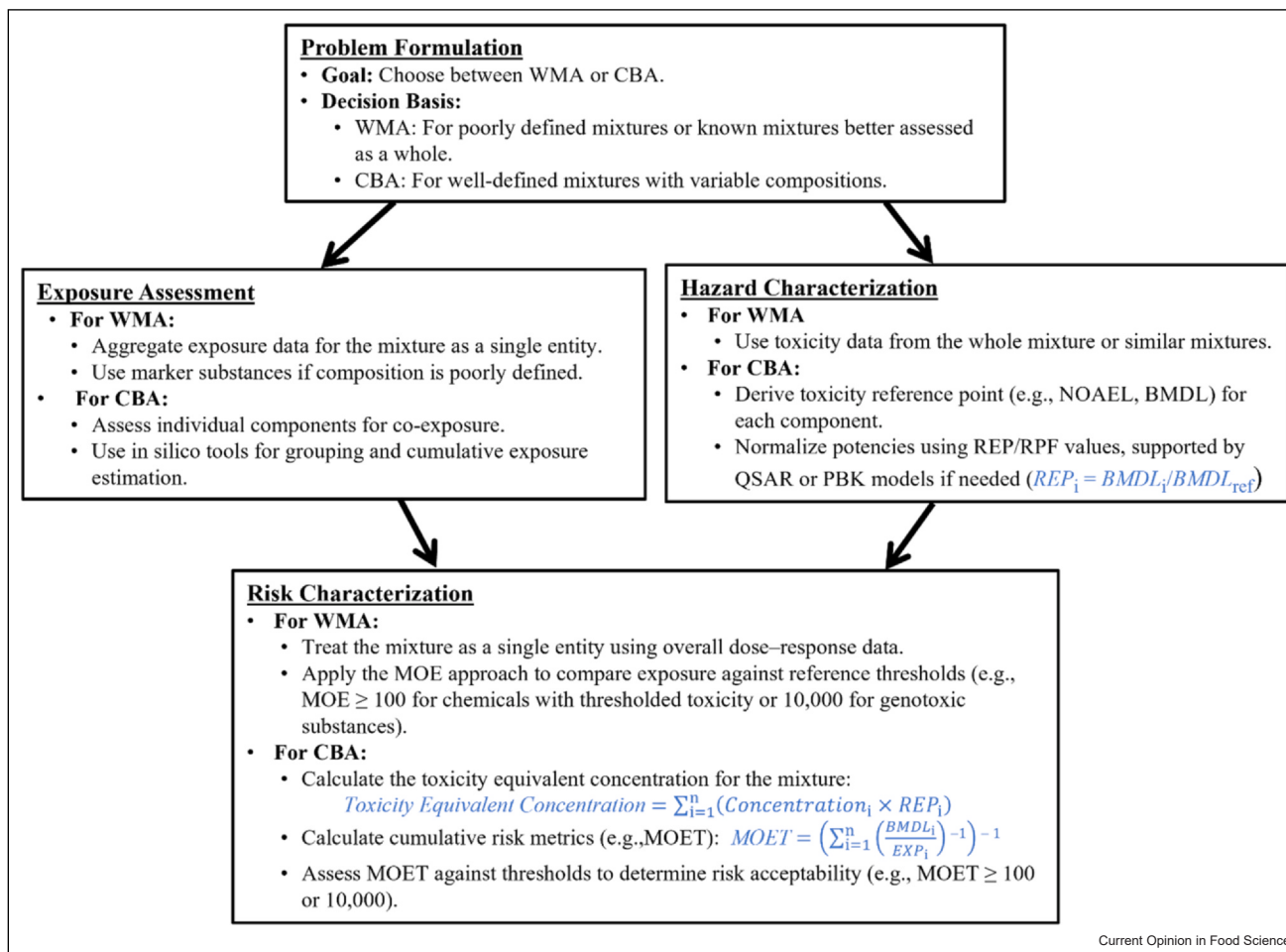
Serious concerns have been expressed by the European Food Safety Authority (EFSA), stating that climate change not only complicates the existing food safety challenges but also introduces new hazards into the food system [6]. For instance, the warming climate promotes the growth of harmful algal blooms, increasing the prevalence of marine and freshwater toxins [4,6]. Additionally, extreme weather events, becoming more frequent and severe, lead to soil degradation and nutrient leaching, which increase crop susceptibility to pests and diseases [6]. This not only raises the potential for mycotoxin contamination but also alters the types of mycotoxins that are prevalent, as climate change drives shifts in the geographical distribution and activity of mycotoxigenic fungi such as *Aspergillus* and *Fusarium* species [7]. These fungi adapt to the new climatic conditions, potentially leading to different mycotoxin profiles in crops [7]. The resulting changes, together with variations in pesticide persistence and efficacy due to changing climate conditions, may necessitate adjustments in pesticide application strategies, including more frequent use or changes in the concentrations or types of pesticides used, potentially leading to higher residue levels in plant products [4,6]. Moreover, changes in environmental conditions also impact the behavior of heavy metals in soils, affecting their solubility and mobility, which could potentially enhance their uptake by crops and increase the levels of these contaminants in plant-based foods [6].

These evolving challenges necessitate adaptive food safety regulations and monitoring systems that can swiftly respond to the growing and novel hazards and risks posed by climate change.

The importance of endogenous formation for the exposome and risk assessment

Another topic gaining momentum in the field of food safety evaluations is the fact that for some compounds, exposure from endogenous formation may contribute substantially to the overall exposure (the exposome) [8]. This holds, for example, for ethanol and methanol and their oxidative metabolites, formaldehyde, and acetaldehyde since these compounds can be formed as physiological components by the intestinal microbiota and by metabolic pathways in human cellular metabolism. In recent years, it has become evident that also various food process-related contaminants can be formed endogenously, including, for example, acrylamide, acrolein, alpha-, beta-unsaturated carbonyl compounds, advanced glycation end products (AGEs) and their aldehyde

Figure 2



Simplified framework for risk assessment of combined exposure to multiple chemicals using a whole mixture approach or a component-based approach [9,10]. WMA: whole mixture approach, CBA: component-based approach, REP_i : relative potency of chemical i , $BMDL_i$: benchmark dose lower confidence limit of chemical i , $BMDL_{ref}$: benchmark dose lower confidence limit of the reference chemical, MOE: margin of exposure, EXP_i : exposure level of chemical i .

precursors methylglyoxal and glyoxal, N-nitroso compounds, ethylene oxide, and furans [8]. The endogenous formation of these compounds is important for food safety assessment because several of these chemicals are putative genotoxic carcinogens, for which it is assumed in risk assessment that the risk increases with each molecule. However, the endogenous formation may serve as a point of reference for risk assessment for the exogenous exposure, and the level of exposure from an exogenous source may appear to be even negligible compared to the endogenous formation. This implies that for such compounds, there would be an apparent threshold, a level of exposure where the risk would not be substantially increased above the background effect caused by the endogenous formation. This may be the case, for example, for not only ethanol but also for formaldehyde, acrolein, acetaldehyde, and AGEs and their aldehyde precursors

[8]. Despite these new insights, the question of what would be considered negligible by risk assessment bodies remains to be answered.

Effects of mixtures and the importance of relative potencies

Another topic of increased attention in modern food safety assessment is the fact that consumers are often exposed to a mixture of chemicals of concern rather than to a single chemical. The combined exposure to multiple chemicals is relevant in, for example, the risk assessment of pesticides, veterinary drug residues, additives, contaminants, etc. EFSA proposed two approaches for the evaluation of combined exposures to multiple chemicals, including a whole mixture approach and a component-based approach (Figure 2) [9]. The

whole mixture approach applies to mixtures of known and also poorly defined compositions, for example, formulated pesticides, biocide products, wastewater effluents, natural flavoring agents, and fermentation products, and treats the mixtures like a single chemical [9]. The component-based approach is applicable for chemically defined mixtures with variability of the mixture's composition in the different exposure scenarios [9]. In the last approach, the components are grouped for assessment based on the similarity in chemical structure, physiochemical properties, hazard characteristics (mode of action and adverse outcome pathways), and exposure considerations. NAMs were recommended for grouping chemicals into mode-of-action-based assessment groups by developing and implementing generic *in silico* approaches such as quantitative structure–activity relationships (QSARs) and physiologically based kinetic (PBK) models [10]. Data on the relative potency (REP) of each component in the mixture are crucial to predict the toxicity of combined exposures of toxicologically similarly acting chemicals. Using REP values or relative potency factors (RPFs), the different toxic potencies of the individual component in a mixture are normalized toward the potency of a reference material (with REP or RPF value equal to 1.0) by multiplying the respective concentration or dose level of the respective chemical in the mixture by its REP or RPF value after which the concentration of the total mixture can be expressed in toxicity equivalent of the reference compound by adding up the obtained normalized concentrations or doses. The REP or RPF values are defined by dividing the toxicity reference point such as a No observed adverse effect level (NOAEL) or lower confidence limit of the benchmark dose (BMDL) of each individual component by that of the index chemical. The REP/RFP methodology allows the cumulative risk characterization on combined exposure of mixtures by calculating the sum of the margin of exposures (MOET), taking the exposure of each component into consideration [9]. Furthermore, previous studies showed the potential for the use of NAMs like PBK models and/or *in vitro* assay to define REP values for, for example, dioxins, PAs, and PA N-oxides [11], enhancing Next-Generation Risk Assessment of combined exposure to multiple chemicals even with limited data.

Per- and polyfluoroalkyl substances

Although PFAS have been used and produced for several decades, they have become a hot topic in food safety only over the last years and are expected to remain important in the near future [12]. The compounds have been in use since the previous century because of their unique physical characteristics being both hydrophobic and oleophobic, providing applications in many fields, including the food industry, where they have been used in, for

example, grease-resistant food packaging and surface-active cooking devices [13]. Because of the strong carbon-fluorine bonds, they are highly resistant to thermal and chemical degradation making them substances that are persistent, bioaccumulative, and toxic and also substances of very high concern [14–16]. Recent years have seen significant revisions in health-based guidance values for PFAS by regulatory bodies, resulting in growing concerns about the risks posed by these persistent chemicals. For example, the tolerable daily intake (TDI) of 150 ng/kg bw per day for perfluorooctane sulfonate (PFOS) and of 1.5 µg/kg bw per day for perfluorooctanoic acid (PFOA) established by EFSA in 2008 [14], were first in 2018 reduced to a tolerable weekly intake (TWI) of 13 ng/kg bw per week for PFOS and 6 ng/kg bw per week for PFOA [15] and in 2020 lowered even further to a group TWI of 4.4 ng/kg bw per week for the sum of four PFAS, including PFOA, PFNA, PFHxS, and PFOS [16]. In contrast, while the Food and Drug Administration (FDA) has not set specific TWI or TDI values similar to EFSA, it has focused on establishing action levels for PFAS in food and consumer products based on the latest toxicological data, aiming to mitigate exposure risks through regulatory oversight [17]. While in earlier risk assessments, estimated human exposure levels were below the established health-based guidance values, with the newly established TWI of 4.4 ng/kg bw per week for the sum of four PFAS set by EFSA in 2020 [16], this was no longer the case. As a result, levels of PFAS in food and drinking water have become a risk management priority. Given this situation and the fact that PFAS are persistent and considered so-called ‘forever’ chemicals, in 2023, the national food safety authorities of Denmark, Germany, the Netherlands, Norway, and Sweden submitted a proposal to the European Chemical Agency (ECHA) for the restriction of around 10 000 PFAS, with the aim to reduce PFAS emissions and make products and processes safer [18].

Adoption and implementation of such a restriction now await the opinions from ECHA's scientific committees for risk assessment and Socio-Economic Analysis. A ban may prove to be needed to reduce current exposure levels, and some initial data show that the voluntary industrial phase-out of PFOS and PFOA in 2000 has resulted in reductions in exposure at the population level [19]. Future efforts in this field also will have to focus on the definition and use of reliable RPFs to enable a refined assessment of combined PFAS exposure, a topic at present leading to substantial debate since it has been argued that the current RPFs proposed by Bil et al. [20] are not robust enough to be used in risk assessment [21–23]. It is expected that the use of *in vitro* and *in silico* NAMs could be of help to define more robust RPFs for the various PFAS, once better insight into their mode of action and relevant critical target organ and effects have been elucidated, likely also with the help of NAMs.

Nanomaterials

Nanomaterials, engineered from diverse chemical constituents, such as silver, titanium dioxide, silicon dioxide, and zinc oxide, have become increasingly integral to the food industry. These nanoparticles are used in a wide range of applications, from preservatives and antimicrobials to flavoring agents and packaging materials, playing a transformative role in enhancing the quality, sensory appeal, shelf life, and safety of food products [24]. Human exposure to these nanomaterials can occur both intentionally, through the consumption of food products containing engineered nanoparticles and unintentionally through contact with packaging materials that release nanoparticles [24,25]. Additionally, these particles can enter the food chain from environmental sources or as byproducts of food processing techniques [24,25]. Public concern over the safety of nanomaterials has heightened due to the growing use of nanomaterials and the limited scientific understanding of key risk factors, such as nanoparticle toxicity, including their genotoxicity, potential for bioaccumulation, unclear exposure levels, and hazards associated with ingestion. Nanomaterials' small size and large surface-to-volume ratio allow them to interact with biological systems in novel ways, which may include the potential to cause DNA damage [26]. This has been particularly observed in studies of metallic, metallic oxide nanoparticles, and fibrous nanomaterials, although inconsistencies in the literature and variations in study design make it difficult to draw definitive conclusions about the physicochemical features and the generation of reactive oxygen species that promote genotoxicity [26,27]. The regulatory landscape is also adapting in response to these concerns. For instance, the use of titanium dioxide (E171) as a food additive in the European Union has been banned since August 2022, following EFSA's scientific opinion that it could no longer be considered safe due to concerns about its genotoxicity [28]. Given the diverse chemical compositions and dynamic properties of nanomaterials, they can undergo transformations throughout their life cycles, influenced by environmental and biological factors, making it impractical to assess every transformation using animal studies for risk assessment. This challenge has driven the adoption of NAMs, as recently highlighted in EFSA's guidance on the risk assessment of nanomaterials, which promotes NAMs in a tiered approach to reduce reliance on animal studies while ensuring comprehensive risk assessments of nanomaterials [29]; however, adapting NAMs to address the specific challenges of nanomaterials for regulatory risk assessment, including potential effects on complex toxicological endpoints remains a significant challenge. Building on the concept of NGRA introduced by Dent et al. [30], Hristozov et al. [31] recently further proposed an NGRA framework for nanomaterials, which integrates NAMs, prioritizing relevant exposure scenarios and combining existing data with targeted testing.

In addition to engineered nanoparticles, micro- and nano-plastics (MNPs) have raised significant concerns over the past year. MNPs have been detected in human food products, including seafood and drinking water, and, more recently, in human blood and maternal and fetal placental tissues [32,33]. This suggests that MNPs can cross the maternal–fetal placental barrier and may reach the fetal circulation. Despite the growing awareness of their presence, our understanding of the health implications and risks associated with MNP ingestion remains even more limited compared to those of engineered nanoparticles. Future research should focus on developing methodologies, drawing from approaches used for engineered nanomaterials, to assess MNP exposure, toxicity, and potential bioaccumulation more comprehensively.

Novel food packaging

The development of novel food packaging materials, such as reinforced bioplastics, metal-organic frameworks (MOFs), and biopolymers, has significantly enhanced packaging functionality and sustainability [34–38]. However, these innovations bring new chemical food safety concerns, primarily due to the migration of substances into food. Reinforced bioplastics, which incorporate nanofillers or additives, may release chemical components under heat or acidic conditions, posing potential food safety risks [34,35]. Similarly, MOFs, incorporated into packaging materials for their ability to enhance antimicrobial activity and selectively adsorb gases like ethylene, present risks of metal ion leaching into food matrices, particularly in moist or acidic environments [36].

Another source of migration that raises new food safety hazards arises from secondary reactions in packaging materials. The Maillard reaction, applied as a cross-linking method in biopolymer films, enhances mechanical and antioxidant properties but may potentially generate reactive byproducts that could migrate into food, raising safety concerns [37]. Similarly, active compounds like plant extracts, added for their antimicrobial and antioxidant benefits, may migrate into food matrices and chemically interact with the polymer or food components, potentially forming secondary substances that warrant further toxicological evaluation [38]. These risks highlight the need for comprehensive studies on chemical stability and migration behavior of these materials to ensure safe application in food packaging systems.

New approach methodologies in risk assessment

As already evident from the topics discussed above, another important development in food safety is the development and use of NAMs [10,11,31,39]. NAMs aim at

Table 1

Overview of relevant representative NAMs in risk assessment.

Type of NAM	Description	Examples/techniques
<i>In vitro</i> models	Experimental models using cultured cells, tissues, or organs to replace animal testing for toxicity and safety evaluation.	2D/3D cell culture models, organ-on-a-chip, stem cell-derived models
Cell-based omics technologies	Techniques to analyze genetic, proteomic, or metabolic responses to chemicals, providing mechanistic insights into toxicity.	Gene expression profiling, RNA-seq, mass spectrometry-based proteomics, metabolomics profiling
Computational modeling	Using algorithms, simulations, and data-driven approaches to predict the physicochemical, toxicokinetic, and toxicodynamic characteristics of chemicals, reducing the need for physical experiments.	QSAR models, PBK models, QIVIVE, machine learning-based prediction tools
Read-across	A data-driven approach to predict the toxicity of untested chemicals based on similarity to tested chemicals.	Structural similarity-based predictions, category formation, analog identification; tools like ToxRead
High-throughput screening	Rapid testing of large numbers of substances or compounds for specific biological activities or toxicological effects using automated technologies.	Automated toxicity screening, enzyme inhibition assays, receptor binding assays
Tissue engineering	Creating three-dimensional tissues or organ models using biocompatible materials to replicate human biology for testing.	3D-printed tissues, scaffold-based tissue models, bioreactor systems for tissue culture
Organotypic cultures	Cultures mimicking the structure and function of specific organs or tissues for real-world biological evaluation scenarios.	Brain organoids, liver spheroids, kidney organoids

enabling risk and safety assessment without the need for animal-based data and encompass various nonanimal testing approaches, such as *in silico* and *in vitro* methods. An overview of relevant representative NAMs is presented in Table 1. This development is driven by the fact that animal experiments are time-consuming, costly, and more and more considered unethical, while at the same time, they may not adequately reflect the human situation and are less suitable for the mechanistic underpinning of toxicity at a molecular level. Thus, also in the field of food safety, there is a large effort to integrate NAMs, based on *in silico* and *in vitro* approaches, into the hazard and risk assessments. This development has in recent years also been accompanied by a call from the food industry to integrate NAMs routinely into scientific and regulatory risk assessment [40]. This regulatory acceptance and uptake require a paradigm shift in risk assessment [39]. A recent review focusing on the use of NAMs in food safety assessments concluded that “Reducing animal testing and filling some RA gaps via NAMs is almost a reality. Moreover, there is a growing body of evidence confirming that the inclusion of mechanistic information improves risk assessments [39].” The relevant *in vitro* and *in silico* methods include QSARs and read-across and PBK modeling to facilitate quantitative *in vitro* *in vivo* extrapolation (QIVIVE), omics technologies, with cell models and PBK models preferably being relevant for the human situation [41]. Recently, EFSA launched the open-access online TKPlate platform [42], aiming at facilitating food safety without animal testing by providing a platform for PBK modeling and predicting the toxicokinetics of a large number of chemicals in humans. At present, the outcomes of TKPlate are not yet used in EFSA’s risk assessments, but it is expected that training of staff and further optimization of the platform will support its use shortly. The outcomes would, for example, be of use in demonstrating target

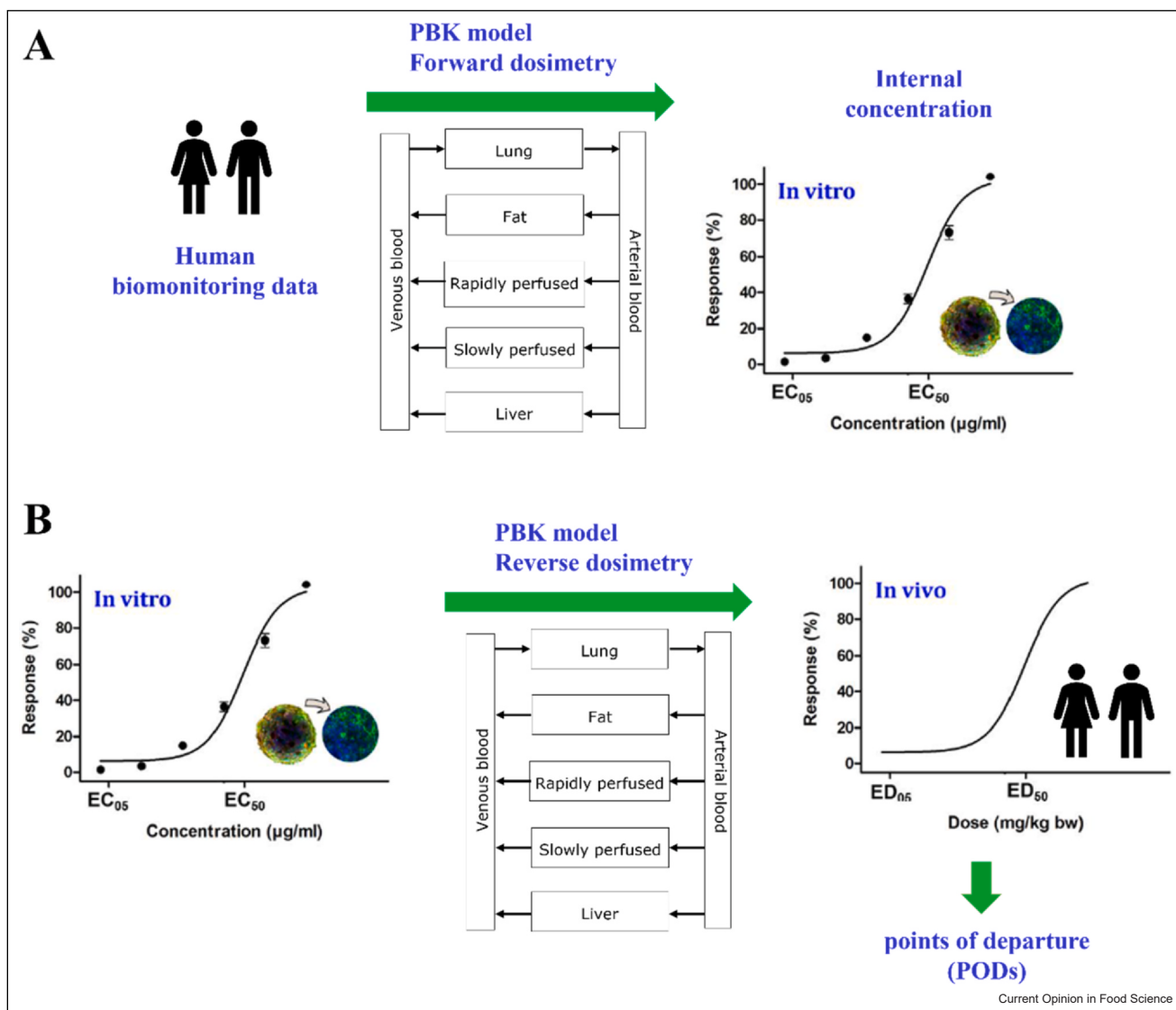
tissue exposure or for forward or reverse dosimetry. Forward dosimetry enables the translation of estimated levels of human exposure to corresponding internal concentrations, which can then be compared to outcomes from relevant *in vitro* bioassays to estimate the likelihood of *in vivo* effects to occur (Figure 3a) [43]. Reverse dosimetry enables the translation of *in vitro* concentration-response data to the *in vivo* situation, thus defining dose-response curves that provide points of departure to define health-based guidance values in risk assessment (Figure 3b) [44].

Artificial intelligence in food safety

AI is becoming increasingly important in the field of food safety, offering significant improvements in how risks are assessed and monitored. AI is particularly effective at rapidly processing large volumes of data, which helps to identify and predict potential food safety hazards that traditional methods might overlook. This ability is especially valuable as food supply chains become more complex and globalized. Moreover, AI’s strength lies in predictive modeling, which enables the early detection of risks by analyzing data on foodborne pathogens, environmental conditions, and supply chain dynamics [45,46]. For instance, in risk assessment, AI-driven *in silico* models can be used as NAMs, offering faster and more ethical alternatives to conventional testing methods [47]. A recent study by Fu et al. [48] highlights how automated read-across technology, that is, the read-across-based structure-activity relationships tool can accurately predict the toxicity of food-related chemicals, thus reducing the need for traditional animal testing.

As the food industry faces new challenges, including those related to environmental changes and emerging contaminants, AI’s ability to analyze diverse data sets

Figure 3



Schematic presentation of the PBK modeling-based forward (a) and reverse dosimetry (b) approaches.

becomes increasingly valuable. It helps assess and predict the impact of factors like climate change and pollutants on food safety, ensuring that safety standards evolve in line with these new challenges [4].

Conclusions

The current review presents some of the current and emerging issues in food safety. The selection made was based on topics raising concern at present and expected to maintain or even gain importance in the near future. These developments are to a large extent driven by the increasing human world population and related consequences, including global warming, environmental pollution, concerns over food security and biodiversity,

and increased use of plant-based foods. In addition, new technological developments as well as new scientific insights bring newly emerging issues to the field of food safety, such as consideration of the exposome and endogenous formation of compounds of concern and NAMs.

The related topics discussed in some more detail in the present review included (i) natural toxins accompanying the use of more plant-based foods to increase the sustainability of our food chain and food security, (ii) effects of climate change, (iii) the role of endogenous formation for the exposome in risk assessment, (iv) effects of mixtures and the importance of relative potencies, (v)

nanomaterials and PFAS as newly emerging risks, and (vi) use of new technologies like NAMs and AI in risk assessment.

The common characteristic of all these food safety issues is the way in which science precedes risk assessment practice, where risk assessment bodies and regulators do take the developments into consideration but take time to shift the risk assessment paradigm. This may in part be due to the fact that relevant data are not yet available. Some developments however show that changes are actually happening or likely to happen in the near future, and these include, for example, the launch of TKPlate by EFSA, the potential ban of PFAS in the EU, and the use of outcomes obtained by NAMs in risk and safety assessment. Other topics of current and emerging concern do still require further data before risk assessment and related risk management practices in food safety will be changed. This includes, for example, the definition of additional methods to evaluate mixture toxicity, of RPFs for PFAS, and of the impact of climate change on mycotoxin levels in plant raw materials and foods derived from them. Moreover, with the rapid development of AI, questions remain on how to effectively utilize AI to reduce or replace animal testing, analyze vast data sets resulting from environmental changes and emerging contaminants, and even predict novel risks in food safety.

Data Availability

No data were used for the research described in the article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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- of special interest
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