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Food contaminants: mechanisms of toxicity, computational assessment, and mitigation

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Understanding the toxicological mechanisms of food contaminants is critical for assessing risks to human health. This review comprehensively examines their adverse effects, tracing the pathway from molecular initiation to systemic organ-level damage. A central focus is placed on the growing trust on computational methods as ethical and practical alternatives to traditional animal testing. The discussion encompasses a multi-scale assessment, detailing atomic-level interactions through Density Functional Tight Binding Molecular docking and Molecular Dynamics (MD) simulations, analyses of toxicity pathway, and prediction of systemic fate using Physiologically Based Pharmacokinetic (PBPK) modeling. We further explore how these *in silico* insights are integrated with experimental data to build predictive models, including Quantitative Structure-Activity Relationship and machine learning frameworks. Ultimately, this review aims to inform the development of effective strategies for mitigating contaminant risks, thereby advancing public health objectives and supporting the 3Rs principles (Replacement, Reduction, and Refinement) in toxicological science.

KEYWORDS

computational modeling, endocrine disruptors, food contaminants, health risk assessment, toxicity

1 Introduction

Chemical contaminants in the food chain, ranging from environmental pollutants to processing by-products, present a persistent threat to human health (Food safety, 2025). Traditional toxicity assessment relying on animal models is increasingly supplemented by advanced *in silico* approaches due to ethical and efficiency demands (Jadhav et al., 2025). This review synthesizes current knowledge on the mechanisms of toxicity of major food contaminants and explores the transformative role of computational tools in predicting their hazard and informing mitigation strategies, thereby shaping a more proactive food safety paradigm (Piparo et al., 2011; Kuppusamy et al., 2024).

Currently, significant efforts are underway in software development to simulate and refine protein interactions in "*in vivo*" media, coupling Molecular Dynamics (MD) and machine learning to predict their stability, interactions and reactivity. As early as 2007, the United States National Research Council proposed that in 21st century, the "*in vivo*" experiments would be substituted by alternative "*in vitro*" assays to assess health risks (Krewski et al., 2010). The effective use of these alternative technologies, such as "*in vitro*" cell tests, hinges on a deep understanding of chemical toxicological mechanisms. This

includes comprehending molecular and cellular toxicity pathways, tissue and organ-level toxicity effects, and gathering comprehensive scientific evidence. Ultimately, this understanding facilitates the generation of adverse outcome pathways (AOPs) at both individual and population levels (Escher et al., n.d.). Following this trajectory of toxicological testing development, food toxicology is actively transitioning from traditional animal experiments to novel *"in vitro"* and *"in silico"* strategies (Yang et al., 2023).

Food contaminants originate from diverse sources, including agricultural chemicals, heavy metals from harvesting lands, mycotoxins, and environmental pollutants like dioxins and Polychlorinated Biphenyls (PCBs). All these can enter the body through contaminated food consumption (Tola, 2025). Reflecting a global shift towards ethical testing, the European Union (EU) implemented a comprehensive ban on cosmetics animal testing in 2013, a trend swiftly followed by countries like Norway, New Zealand, and Israel in 2013, and India and Brazil in 2014 (Sreedhar et al., 2020).

The application of computational methods to predict toxicology has surged, driven by the ethical and costs limitations of traditional experiments coupled with ever-increasing computational capacity. These advancements offer quicker insights into society's growing concerns about food toxicity. Traditional approaches are often constrained by the limited number of doses, time points, organ systems, and combinations that can be realistically tested in a single laboratory experiment. While toxicity regulations demand reproducible assays, experimental methods frequently encounter limitations due to fragmented standardization and inherent variability in conditions, which can be influenced by factors as simple as reagent batch differences or purchase dates.

Advances in computer science promises not only faster experiments but also more robust reproducible results. Furthermore, computational modelling and simulations can connect fields like statistics, chemistry and physics enabling the prediction of outcomes in processing methods with sufficient accuracy to design more effective experimental assays, thereby saving both time and cost (Smith et al., 2022).

Molecular dynamic (MD) simulation stands out as one of the most widely used and promising computational methods (Cavaliere et al., 2020; Zhang et al., 2020). MD simulation has exhibited its outstanding advantages in the design and study of novel drugs, proteins and advanced materials. For instance, MD studies have elucidated the H-bonding interaction between paracetamol and water, revealing how this interaction promotes the solubility of paracetamol (Xu et al., 2018). Sadeghi and co-workers explored the radial distribution functions (RDFs) and spatial distribution functions (SDFs) of ionic liquids *via* MD study (Nian et al., 2021), and suggested that strong interactions between anions and cation can promote anions distributed around cations evenly. Similarly, MD studies exploring the secondary structure and activity of lipase in natural deep eutectic solvents found that lipase can be activated through the H-bond binging interactions (Nian et al., 2021).

In the field of food sciences, molecular simulation technology has mainly been applied to proteins, lipids and carbohydrates. These food components are often combined with other substances and processed to improve their functional properties. MD simulations were first applied to carbohydrates in 1986 by introducing this technology to understand the relationship between carbohydrate structure and its function (Wang et al., 2022). Due to limitations of computer hardware, resources, performance and MD simulation software, the initial simulation could only use 6, 7 or 8 glucose units to represent single chain starch molecules. Related studies showed that the bond length of a virtual angle formed by O4–O4′- O1′ could describe the change in twist angle of glucose residues. Koehler *et al.* in 1988 studied the configuration change of α-cyclodextrin in aqueous solution by MD simulation, but the simulation time was only tens of picoseconds (Wang et al., 2022). Another important factor coupled with the MD simulations is the level of theory used for the calculations of atomic forces, beyond classic force fields. The development and improvement of electronic structure calculation methods based on or derived from quantum mechanics, as is the case of the Density Functional Tight Binding (DFTB) theory, and the ever-growing computational capabilities in supercomputing in recent times, makes it possible nowadays to simulate dynamics models that were unthinkable a few years ago (in DFTB one can easily scale up to 5,000–10,000 atoms systems using) (Çetin et al., 2024). Such techniques, which are 3,000 to 30,000 times faster than regular Density Functional Theory (DFT), allows considering more realistic sizes and conditions such as molecules solvation or molecule adsorption on surfaces. In recent years, some of the aforementioned techniques based on MD have been successfully applied to investigate nanosized titania with sizes 2.2–4.4 nm (Mikolajczyk et al., 2023).

For the evaluation of food toxicity, we must focus our attention on particles added to food as ENMs. Physicochemical characteristics of ENMs are the key determinants of their techno-biological functionality, as well as the source of potential adverse health effects. A list of such physicochemical properties has been defined by the Organisation for Economic Co-operation and Development (OECD). Amongst these parameters the size, chemical composition aggregation agglomeration state, and surface treatment/coating of ENMs appear to be most critical for nanotoxicity issues. Parameters that can be perfectly estimated by computational methods within the MD framework.

In this review, we aim to present the different tools based on MD to study fundamental atomic interaction and simulate the interaction of ENMs and other common particle present in food with proteins and other biomolecules. We will examine MD techniques such as DFTB, Molecular docking and Virtual Screening, where protein–small-molecule interactions are essential for the sustainability of biological processes such as enzymatic catalysis and overall homeostasis in the body. These is a good technique to analyze the architecture of compounds generated by two or more distinct molecules. Additionally, we will analyze the interaction between chemical compounds and their target protein receptors at the atomic level, which is an effective tool in drug design and provide a good estimation of

Abbreviations: BPA, Bisphenol A; ENMs, Engineered nanomaterials; ENPs, Engineered nanoparticles; NPs, Nanoparticles; MD, Molecular dynamics; PBPK, Physiologically based pharmacokinetic modelling; DFTB, Density functional based tight binding; QSAR, Quantitative structure-activity relationship; ML, Machine learning; AOP, Adverse outcome Pathway; NAMs, New approach methodologies.

the binding (Maden et al., 2022; Keval and Tejas, 2022). Also, we want to mention Molecular dynamics simulations and MM-PBSA, a popular approach to estimate the free energy of the binding of small ligands to biological macromolecules (Genheden and Ryde, 2015; Tuccinardi, 2021), by combining molecular mechanics calculations and continuum solvation models (Hou et al., 2011). It is more computationally efficient than the related approach, the linear interaction energy (LIE) method, which averages interaction energy from the MD simulations to estimate the absolute binding free energy. It has been successfully applied to various protein–ligand (Hou et al., 2002; Stoica et al., 2008) or protein–protein/peptide complexes (Hou et al., 2006).

We want to go a step further in the field of toxicology and the calculation of physical and chemical properties with MD. These can subsequently be used as descriptors for Quantitative Structure-Activity Relationship (QSAR) toxicology models or to feed new models based on Artificial Intelligence. The proposed computational approach is in line with the 3R principles (Reduction, Replacement and Refinement) for animal testing and contributes to the development of alternate testing methods and the implementation of intelligent testing strategies (Escorihuela et al., 2018a). The OECD has established principles and guidance for validating and using QSAR models for regulatory purposes, ensuring they are scientifically robust and reliable. This guidance has led to the increasing acceptance of QSAR predictions in various regulations related to chemical substances, including those under REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) ((Q)SAR Assessment Framework: Guidance for the regulatory assessment of (Quantitative) Structure Activity Relationship models, predictions, and results based on multiple predictions Series on Testing and Assessment No. 386, 2023).

To provide a comprehensive understanding of how chemical substance moves through the body (absorption, distribution, metabolism, and excretion) by incorporating physiological and biochemical information we must also mention the Physiologically based pharmacokinetic (PBPK) models (Pletz et al., 2020), PBPK models can incorporate various levels of physiological complexity and drug elimination and distribution processes depending on the intended use and the available knowledge of the drug's characteristics (Isoherranen, 2025).

2 Engineered nanoparticles and other contaminants in food

According to the European Food Safety authority. NM refers to any intentionally produced material that has one or more dimensions of the order of 100 nm or less in one or more dimensions, composed of discrete functional parts and including structures, agglomerates or aggregates, which may have a size above the order of 100 nm but retain properties characteristic of the nanoscale. Moreover, ENM that contain <50% nanoparticles by number are not considered nano by certain regulatory agencies (e.g., European Food Safety Authority, EFSA), who is the responsible for the risk assessment of the use of nanomaterials in food and feed, as well as in food contact materials, other agencies such as Food and Drug administration in EUA (FDA), do not have a percentage in the specifications (Sohal et al., 2018).

The physicochemical properties of nanomaterials can differ significantly from those of their bulk counterparts. Although these differences confer important technological advantages, ENMs may also pose potential risks to human health and the environment. Evaluating their potential hazards requires a thorough characterization of surface structure, physicochemical properties, and reactivity, as these factors determine how ENMs interact among them and with environmental components. In particular, surface characteristics, tendency of nanoparticles to aggregate, which directly affects their environmental fate and exposure potential. Moreover, aggregation can alter surface properties, thereby modifying interparticle interactions and influencing overall reactivity (Mikolajczyk et al., 2023).

The physicochemical properties in general, as size, roughness, surface area of NPs have a great impact on their toxicity since they can change the mechanism of toxicological response given accumulation, uptake, and trans-location inside the cell, by organelle or membrane uptake. One single material with different shapes and sizes can considerably change the response of live tissue and identify NPs as a safe or toxic (Attarilar et al., 2020).

For instance, size-related changes in particles smaller than 5 nm are more pronounced than those observed in particles ranging from 15 to 90 nm, primarily due to quantum size effects. One particularly relevant phenomenon associated with smaller NPs is their ability to penetrate biological systems directly, where they can dissolve and release toxic metal ions—a mechanism known as the "Trojan horse" effect (Stenzel, 2021). This effect is specific to nanoscale materials and results from their inadvertent recognition and uptake by cellular receptors (Escorihuela et al., 2018a).

The European Union Observatory for nanomaterials (EUON) (https://euon.echa.europa.eu/food1) also has a specific webpage for food and food packaging, novel food and even for Nanomaterials in active and intelligent food contact materials where we can find EU regulations. *EUON* published on 22 October 2024, reviewed the release of nanoparticles from consumer products, including from food contact materials (FCMs), and their potential toxicity (Abram et al., 2025).

Food industry uses ENM for multiple functional applications to enhance flavours, colours, as food additives, food packaging, as antimicrobials for improving food preservation, for nutrient encapsulation and enhancing bioavailability, and in agricultural practices to enhance food quality, safety, nutrient delivery, and production yield (Zhang L. et al., 2025).

Accordingly, the current *EUON* report finds that applications of nanomaterials in packaging have significantly increased in the past decades increasing the human exposure and related impacts. For FCMs, the concern pertains to nanoparticles migration into the food, leading to human exposure. While the nano-size and high surface area-to-volume ratio of the particles bring advantages to materials such as resistance, flexibility, or thermal conductivity their small size also has drawbacks, such as the ability to cross biological membranes (Gupta et al., 2024).

For instance, SiO_2 is used as colour additives, flavours, packaging, and anticaking agents in powdered foods. Nanoparticles are also effective carriers for fragrances and flavoring agents. In addition to flavour enhancement, ENMs are also employed to improve food appearance, for instance, titanium dioxide (TiO_2) is approved as a food colorant, with regulatory limits

typically set below 1% w/w. TiO_2 is also used as a food additive and flavour enhancer in a variety of non-white foods, including dried vegetables, nuts, seeds, soups, and mustard, as well as beer and wine. Titanium dioxide in nanoform is an antimicrobial agent, sometimes in combination with other compounds or elements as nickel oxide and cobalt, for the inactivation of foodborne pathogens. TiO_2 also serves as an active component in packaging due to its inert nature and low toxicity. Mechanistic studies indicate that under ultraviolet (UV) irradiation, TiO_2 generates reactive oxygen species (ROS), including hydrogen peroxide, hydroxyl radicals, and superoxide anions. These species can disrupt microbial cell walls, providing a potent antimicrobial effect (Sharma et al., 2023; Ameta et al., 2020).

The properties of ENMs enable their applications as food additives, functional food carriers, in active and intelligent packaging materials, and in agricultural practices to enhance food quality, safety, nutrient delivery, and production yield. In solution, nanoparticle-based sensors, array biosensors, electronic noses, nano-test strips, and nanocantilevers are among the different types of nanosensors used for packaging (Biswas et al., 2022; Anjum et al., 2023). These include sensors capable of detecting foodborne pathogens such as *Escherichia coli* and *Salmonella*, or the controlled release of antimicrobial agents (Suvarna et al., 2022). For example, silver-based nanocomposites have a strong antibacterial activity. However, zinc oxide (ZnO) nanoparticles are considered significantly less toxic to humans and animals than silver nanoparticles (Ag NPs), and thus offer a safer alternative. ZnO is frequently used in cosmetics, medical devices, drug delivery systems, UV light absorbers, active packaging, additive in supplements, antimicrobial, and antifungal. The United States Food and Drug Administration (FDA) currently recognizes ZnO as "generally recognized as safe" (GRAS) (Espitia et al., 2013).

Another example of nanoparticles used in food industry are Carbon NanoTubes (CNTs), used as a nanosensors, active packaging, antibacterial or antifungal, they absorb undesirable flavors, as well as in low-resistance conductors and catalytic reaction vessels, gelation, and as viscosifying agent (Ashfaq et al., 2022; Fuciños et al., 2019).

Iron, in the form of iron oxide, is mostly used as a food colorant (Sieg et al., 2024). Iron nanoparticles are a health-promoting food additive since iron deficiency is one of the most common micronutrient deficiencies worldwide. The solubility and the bioavailability of poorly acid-soluble iron compounds can be improved by decreasing their primary particle size and thereby increasing their specific surface area (Hilty et al., 2011; Hilty et al., 2011; Hilty et al., 2011; Hilty et al., 2011).

For instance, SiO_2 nanoparticles, or silica nanoparticles have been reported to act as effective carriers for fragrance and flavoring agents, anti-caking agent or stabilizer (Zhang et al., 2023).

Another important effect of ENM is the nano-encapsulation, which involves the incorporation, absorption or dispersion of bioactive compounds in or on nano-sized vesicles. This may protect the bioactive compounds against degradation, improve stability and solubility (e.g., solubilizing a hydrophilic compound in hydrophobic matrices and *vice versa*) leading to increased bioavailability and delivery to cells and tissues (Peters et al., 2016; Peters et al., 2016; Peters et al., 2016; Peters et al., 2016; Mallia et al., 2022).

Due to the specific ENM physicochemical properties and high reactivity, ENM can influence basic cellular processes, such as proliferation, metabolism, and death. A report by the British Royal Society notes that we may face a nanotoxicity crisis in the future (The Royal Society et al., 2004). Only with a proper detailed understanding of the properties of nanomaterials like size, solubility, surface chemistry, composition, *etc.*, we will be in a position to find useful and safe food products. Exist a gap in the lack of Reference Materials (RM) or reference test materials (RTMs) for NM characterization in complex media such as food, consumer products and other matrices. Current RMs fail to reflect the complexity of these materials, making it difficult to ensure consistent and accurate testing across different types of NMs and NM matrices, thus hindering innovation and compliance (Abram et al., 2025).

To make us and idea about the use on ENM in food we can check the data available in the Nanotechnology Product Database (https://product.statnano.com/) where are reported the use of nanomaterials in food products by countries, among many other data available to evaluate.

On the other hand, we focused also with BPA, that contaminates food through migration from polycarbonate plastic containers and the epoxy resin linings of metal food cans. This endocrine disruptor is linked to health problems including diabetes, obesity, and potential issues with reproduction and the brain. The values of BPA in food in Europe has been changed from 2025 by the EFSA, this agency has lowered the tolerable daily intake (TDI) for BPA respect to 2015, around 20,000 times lower (Bisphenol A in food is a health risk|EFSA, 2023).

3 Molecular mechanisms of toxicity

The physicochemical properties of nanomaterials and reactivity can differ significantly from those of their bulk counterparts. Although these differences confer important technological advantages of ENMs may also pose potential risks to human health and the environment.

Evaluating their potential hazards requires a thorough characterization of surface structure, physicochemical properties, and reactivity, as these factors determine how ENMs interact with one another and with environmental components (Mikolajczyk et al., 2023).

Recent studies have provided deeper insights into the size-dependent behaviour of nanoparticles, demonstrating that smaller nanoparticles (NPs) tend to show greater variability in their properties and reactivity, whereas larger NPs exhibit more consistent behaviour (Faria et al., 2015). One particularly relevant phenomenon associated with smaller NPs is their ability to penetrate biological systems directly, where they can dissolve and release toxic metal ions—a mechanism known as the "Trojan horse" effect. This effect is specific to nanoscale materials and results from their inadvertent recognition and uptake by cellular receptors (Escorihuela et al., 2018b).

For non-nano contaminants like mycotoxins, pesticides, and industrial chemicals such as BPA and its analogs, toxicity primarily arises from compound-specific mechanisms. These include metabolic activation (Heikkinen et al., 2025), receptor-mediated

disruption of endocrine signaling (Tang et al., 2025), and direct macromolecular damage. The Organisation for Economic Co-operation and Development (OECD) defined a list of physicochemical properties to assess the nanotoxicity of nanomaterials that can be determined by MD simulations. Amongst those parameters one finds the size, chemical composition, aggregation agglomeration state, and surface treatment/coating of ENM appear to be most critical for nanotoxicity issues. Due to the specific ENM physicochemical properties and high reactivity, ENM can influence basic cellular processes, such as proliferation, metabolism, and death. Individual ENMs may lead to one or more toxicity endpoints, resulting in dysfunction of these basic processes. In recent years, several *"in vitro"* studies have assessed the potential adverse health effects of ENMs, and the main toxicity mechanism identified are:

3.1 Ability to induce oxidative stress species (ROS)

The most relevant pathogenetic pathway linking ENM exposure to tissue damage is represented by the induction of reactive oxygen species (ROS) generation (Liu et al., 2013). Oxidative stress arises when there is an imbalance between (ROS) production and the body's ability to neutralize or repair the damage caused by these species. The ENM contaminants often induce ROS production, which can harm cellular macromolecules such as lipids, proteins, contributing to diseases such as inflammation in tissues or even cell death. Additionally, ENM can affect immune responses by altering immune cell function, leading to immune suppression or autoimmune disorders (Gosslau, 2016; Tola, 2025). ROS are highly reactive molecules—this includes moieties such as the superoxide anion (O^{2-}), hydrogen peroxide (H_2O_2), and hydroxyl radicals ($OH^{\cdot}$)—and play a crucial role in cellular signalling, but have the potential of being harmful when generated excessively. They release toxic ions and cause the oxidative stress, disrupt electron/ion cell membrane transport activity and cause oxidative damage and lipid peroxidation, whereas results from *"in vivo"* studies have shown that these materials can induce adverse effects on the respiratory, cardiovascular and nervous systems. Literature demonstrated that ZnO NP and Ag NP used as antimicrobial to food packaging and carbon nanotubes (CNT) can elevate intracellular ROS levels triggering oxidative stress ractions (Zhang L. et al., 2025). ROS also induce to cellular disfunction damaging lipids, proteins, and even DNA.

Other common toxicity endpoints involve cytotoxicity and genotoxicity (Martirosyan and Schneider, 2014). Prolonged oxidative stress has been linked to chronic inflammation, which plays a crucial role in the pathogenesis of various diseases, including cancer, neurodegeneration, and cardiovascular disorders (Batir-Marin et al., 2025). Studies have shown that zebrafish embryos exposed to Ag NPs, TiO_2 NPs, and CdSe quantum dots exhibit significant generation of ROS, leading to apoptosis and developmental abnormalities (Batir-Marin et al., 2025). Reduced NP size correlates with increased ROS generation and toxicity in aquatic organisms, including zebrafish. For instance, silver nanoparticles (Ag NPs) smaller than 10 nm trigger higher oxidative stress levels compared to larger particles due to their enhanced cellular penetration and bioavailability (Flores-López et al., 2019). Similarly, titanium dioxide (TiO_2) NPs of <20 nm induce significant ROS production and mitochondrial dysfunction in zebrafish embryos (Faria et al., 2015). Another example is SiO_2, where the toxicity of SiO_2 nanomaterial has been evaluated "*in vitro*" and "*in vivo*" (Perez-Borm et al., 2006; OECD, 2004) no acute toxicity of amorphous SiO_2 after conducting a toxicity study. But a recent study showed that fumed SiO_2, a form of synthetic amorphous silica, produced reactive oxygen species (ROS) and caused red blood cell hemolysis (Yang et al., 2016).

And other recent work conclude that cytotoxicity and organ damage caused by SiO_2 NPs vary and are affected by many factors, including the SiNP type, particle size, pore size, degree of modification, dosing frequency, dosage, and administration time. And the toxicity mechanisms of this NPs include oxidative stress, inflammation, and apoptosis; however, research on the involved signal pathways remains relatively incomplete (Huang et al., 2022).

3.2 Surface charge and coating, surface reactivity

The surface charge of ENMs affects their interaction with biological membranes and proteins. The size of nanoparticles is a very important feature, crucial role in their toxicity potential, for its unique properties as the surface area of engineered nanoparticles (ENPs) depends upon its size (Ameta et al., 2020). Small NPs exhibit higher surface-area-to-volume ratios, increasing their reactivity (Batir-Marin et al., 2025). In general, positively charged ENPs interact more easily with cell membranes due to electrostatic attraction to the negatively charged cell membranes, leading to increased cellular uptake and higher cytotoxicity compared to neutral or negatively charged ENMs (Zhang L. et al., 2025). Surface coatings are applied to ENPs to modify their properties, such as improving stability, dispersibility, and biocompatibility. Common surface coatings include polymers (e.g., Poly-ethylene-glycol or PEG), surfactants (e.g., Tween 80), and inorganic materials (e.g., silica). These coatings can alter interactions with biological systems, potentially influencing their toxicological profiles. For instance, PEG modification, is often employed to reduce toxicity. One study demonstrated that PEG-coated Ag NPs exhibited lower cytotoxicity, immune activation, and tissue damage compared to uncoated Ag NP (Bastos et al., 2016). When NPs enter biological environments, such as zebrafish media or blood plasma, they rapidly adsorb proteins and other biomolecules on their surfaces, forming a dynamic protein corona. This corona can significantly alter nanoparticle properties, including surface charge, hydrodynamic diameter, colloidal stability, and cellular interactions, ultimately affecting biodistribution, oxidative stress responses, and toxicity profiles (Liu et al., 2025).

3.3 Solubility

Solubility is another key physicochemical property that warrants particular consideration and impacts ENM endpoint toxicity, as it affects how they interact with cells, tissues, and the environment. Insoluble or partially soluble ENMs in the digestive fluids, draw

more attention due to their potential to cross the gastrointestinal tract as an intact particle. As stated by the EU Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), free and low solubility ENMs are a priority concern for human and environmental safety (Martirosyan and Schneider, 2014).

When nanoparticles finally dissolve, they can release toxic ions or change their size, surface area, and overall chemical behavior (Eisenbrand, 2020a). Solubility and speed (rate) of dissolution are dependent on a particle's chemical and surface properties, as well as size, and are further impacted by the surrounding media. The potential for NPs to dissolve can effectively influence their persistence in the environment and act as a critical control on their biological response. Although size is considered as the primary physicochemical property affecting solubility of NPs, various other parameters such as, surface area, surface morphology, crystallinity and crystal structure also need to be considered, as the strength of the surface bonds, their spatial arrangements as well as the presence of impurities, and storage conditions may influence NPs dissolution (Misra et al., 2012; Eisenbrand, 2020b). For example, if NPs aggregate and sediment, they become available to sediment dwelling organism and can enter through dietary uptake.

Similarly, if the NPs dissolve in the exposure media, speciation of ions with other ligands can be prominent and the uptake mechanism of ions in organisms will be different. NPs that resist complete dissolution in the media can have a combination of possible routes, *viz.* Endocytosis of NPs, or ion transportation of the dissolved components or a combination of both. There may be another scenario, where NPs associated with the biological membrane can act as a reservoir of metal ions, which are released at a variable rate when NPs undergo dissolution. It is also worth noting that studying NPs' dissolution is not only important for correct interpretation of nano-toxicological data, but can also help in the current move towards "safety by design of NPs" For example, surface functionalization of carbon nanotubes (e.g., using PEG) can facilitate their solubility and thus reduce their biopersistence and any potential toxicity (Misra et al., 2012). It is generally assumed that solubility may increase as particle size decreases, as described by Ostwald–Freundlich equation (Equation 1), correlating interfacial tension and solubility:

$$\frac{s}{s(bulk)} = \exp\left(\frac{4\gamma V}{RTd}\right) \quad (1)$$

Equation 1. Ostwald Freundlich equation. Where s is the solubility ($mol{\cdot}kg^{-1}$) of spherical particles, d (m) diameter, g ($mJ{\cdot}m^{-2}$) is the interaction energy, V is the molar volume ($m^{3}{\cdot}mol^{-1}$), R gas constant ($mJ{\cdot}mol^{-1}\ K^{-1}$) and T(K) temperature (Escorihuela Martí, 2019).

In the case of CuO NPs, experimental data shows an increase in dissolution (rate of dissolution and equilibrium concentration) with reduction in particle size. For ZnO NPs, on the other hand, does not seem to be any significant difference in dissolution between nanoparticles and bulk particles (micron sized particles). Ag NPs present a more complex scenario, which is primarily because size control in the case of metallic Ag NPs is often achieved using surface modifications (Misra et al., 2012). Depending on the NPs' status within the surrounding media with respect to their dissolution behaviour (i.e., which of the following combinations will be present: NPs/ions; ions/complexes; suspended/agglomerated NPs) their bioavailability, uptake rates and toxicity will vary, if NPs aggregate and sediment on release, they become available to sediment dwelling organism and can enter through dietary uptake.

3.4 Genotoxicity and DNA damage

Genotoxicity refers to the capability of chemical agents to damage DNA, leading to mutations, chromosomal aberrations as well as disrupted cellular processes (Kopp et al., 2018; Woo et al., 2011). Food contaminants exert genotoxicity through reactive metabolites, oxidative stress and direct binding to the DNA that will leads to the serious health effects (Payros et al., 2017; Woo et al., 2011). Contaminants present in food such as mycotoxins including aflatoxin B1 and ochratoxin A (Corcuera et al., 2015), by products of processed food such as acrylamide (Eisenbrand, 2020b), heavy metals like arsenic, cadmium, and lead, pesticide residues, and environmental pollutants are responsible for genotoxicity (Dimitrijević et al., 2023; Salvagni et al., 2011; Sherif et al., 2023). MD simulations revealed dynamic aspects of guanine-TiO2 interactions, suggesting surface-induced chemical transformations such as guanine dehydrogenation catalytically mediated by the surface, which may contribute to genotoxic effects (Çetin et al., 2024). Additionally, emerging threats such as nanoplastics and BPA alternatives have become a growing concern in recent years (Sendra et al., 2023; Tang, 2025).

3.5 Endocrine and receptor-mediated effects

Another ENM public health concern is their ability to disrupt endocrine functions through receptor-mediated pathways (Peivasteh-roudsari et al., 2023), (Chemical contaminants in food and feed|EFSA, 2021) These endocrine-disrupting chemicals (EDCs) interfere with hormone signalling even at low exposure levels, contributing to diverse health issues ranging from developmental disorders to cancer (Ahn and Jeung, 2023; Özel and Rüegg, 2023). Food contaminants or toxic chemicals present in food can exert their effects through interactions with nuclear receptors (Paramasivam et al., 2024). These interactions can alter the normal function of the receptors, leading to various diseases. Key nuclear receptors include, among others, estrogen receptors, androgen receptors, and pregnancy X receptor (Paramasivam et al., 2024; Ahn and Jeung, 2023; Liang et al., 2023).

BPA is a well-recognized food contaminant and endocrine disruptor found in the environment. It binds to multiple nuclear receptors, disrupting their normal functions (Goksøyr et al., 2024; Yuan et al., 2023). In addition, other food contaminants such as polychlorinated biphenyls (PCBs), dioxins, and pesticides can also affect nuclear receptors and their functions. Furthermore, BPA alternatives used in industry may also interact with nuclear receptors (Goksøyr et al., 2024; Troisi et al., 2020; Pathak et al., 2024; Pathak and Kim, 2024). These interactions are associated with several health issues, including neurodevelopmental, reproductive, metabolic, and other hormone-related disorders (Ahn and Jeung, 2023). Additionally, food contaminants can cause non-receptor-mediated effects by inhibiting enzymes, altering DNA methylation,

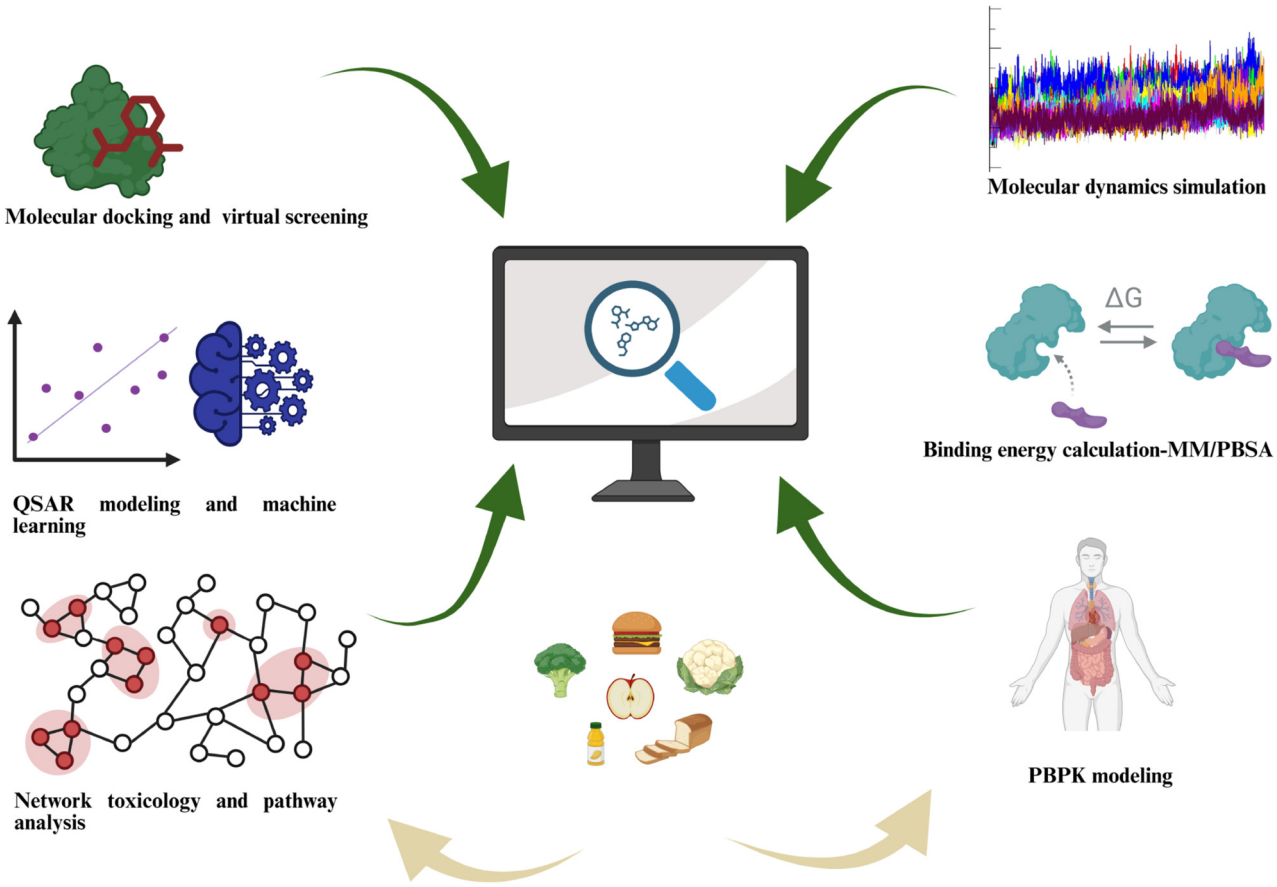

FIGURE 1
Key computational methodologies for *in silico* toxicology and risk assessment of food contaminants. The depicted approaches form a complementary toolkit: molecular docking, QSAR, and machine learning enable high-throughput hazard prioritization; network toxicology elucidates mechanistic pathways; while molecular dynamics with MM/PBSA provides detailed biophysical validation. These inform PBPK models for quantitative exposure and risk prediction, building an integrated animal-free safety assessment strategy.

and affecting cell proliferation and metabolism through activation of G protein-coupled estrogen receptors (Ahn and Jeung, 2023).

3.6 Immune disruption and apoptosis

Food contaminants have a major impact on the immune system and cellular integrity, making them a serious and expanding hazard to human health (Zahir et al., 2025). These environmental pollutants affect apoptosis and impair immunological function, which leads to a variety of issues related to health (Zhang Y. et al., 2024; Suzuki et al., 2020; Winans et al., 2011). Aflatoxins play a significant role in cancer development by affecting various biochemical and molecular pathways. These involve causing direct DNA damage and mutations, and responsible for suppressing apoptosis, weakening the immune system, and triggering epigenetic changes (Mafe and Büsselberg, 2024; Dai et al., 2022).

2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) is one of the most well-studied immunotoxicants, and early research established its key role in shaping the field of developmental immunotoxicology (Winans et al., 2011). Exposure to TCDD during pregnancy has been shown in rodent studies to alter immune development in the offspring (Vos and Moore, 1974; Winans et al., 2011). TCDD-exposed offspring also exhibit weakened responses to influenza virus, including reduced clonal expansion of effector lymphocytes, lower IFNγ levels, and reduced antibody production (Vorderstrasse et al., 2004; Vorderstrasse et al., 2006; Winans et al., 2011). Additionally, polychlorinated biphenyls (PCBs) and polycyclic aromatic hydrocarbons (PAHs) show immunotoxic potential based on human epidemiological data (Winans et al., 2011). Research suggests that inappropriate activation of the aryl hydrocarbon receptor (AhR) pathway by environmental toxicants such as TCDD, PCBs, and PAHs disrupts normal immune system development (Winans et al., 2011).

4 *In silico* approaches for food contaminant risk assessment

In silico approaches provide valuable tools for evaluating the possible risks of food contaminants (Raies and Bajic, 2016). Techniques like molecular docking and virtual screening help researchers predict how contaminants might bind to biological targets, offering early clues about their toxicity (Trisciuzzi et al., 2018). Molecular dynamics simulations take this further by

TABLE 1 Summarizes key computational platforms used for prediction, evaluation, and risk assessment of food-derived contaminants and toxins.

S.No.	Software name	Role in risk assessment	Example use in food contaminant assessment	References
1.	AutoDock vina	AutoDock Vina helps investigate the binding energy of toxins with human target receptors and determine their interaction mechanisms. It also helps in visualizing toxin–receptor interactions.	Docking of aflatoxin B1 or other contaminants to liver receptors	(Eberhardt et al., 2021) (Iori et al., 2024)
2.	Glide	Glide predicts toxin-receptor binding energy with accuracy, provides mechanistic insights, and enables detailed visualization of docking poses.		(Friesner et al., 2004; Desmond|Schrödinger Life Science, https://www.schrodinger.com/platform/products/desmond/)
3.	Gromacs	Gromacs is used to simulate how toxins bind to receptors, revealing changes in receptor stability, conformational dynamics, and binding interactions over time.	MD simulation of BPA with nuclear receptor to study binding stability.	(Páll et al., 2020; Li et al., 2015; Abraham et al., 2015)
4.	Desmond	Desmond enables high-performance molecular dynamics simulations to analyze the stability, conformational flexibility, and interaction profile of toxin–receptor complexes over time.		(Desmond|Schrödinger Life Science, https://www.schrodinger.com/platform/products/desmond/)
5.	g_mmpbsa	Used to estimate the binding free energy of toxins using MM-PBSA calculations on trajectory data generated from Gromacs simulations.	Calculating the binding energy of BPA and other food contaminants with human receptors	(Cherian et al., 2020; Mengeling et al., 2025)
6.	gmx_mmpbsa	gmx_MMPBSA is a tool used to calculate the binding free energy of toxins using trajectory data generated from Gromacs. It supports both MM/PBSA and MM/GBSA methods.		Valdés-Tresanco et al. (2021)
7.	OECD QSAR Toolbox	It is a computational platform for predicting toxins using read-across, QSAR models, and to fill data gaps.	Profiling of food contaminants for toxicity analysis	(Kutsarova et al., 2021) (OECD QSAR Toolbox|https://www.oecd.org/en/data/tools/oecd-qsar-toolbox.html)
8.	Cytoscape	Cytoscape is used to visualize and analyze molecular interaction networks, helping identify key targets involved in toxin-induced health risks.	Analyse the carcinogenic mechanisms of food contaminants such as herbicide residues through network toxicology	(Cytoscape: An Open Source Platform for Complex Network Analysis and Visualization, n.d.; Otasek et al., 2019; Chen et al., 2025)
9.	MATLAB	Matlab's SimBiology toolbox enables PBPK modeling to simulate toxin distribution across tissues, supporting pharmacokinetic analysis.	Risk assessment of chemical contaminants such as drug residues in food.	(SimBiology - MATLAB, https://es.mathworks.com/products/simbiology.html) (Dede et al., 2018)
10.	PK-Sim	It is a PBPK modeling software that simulates toxin distribution, metabolism, and elimination across tissues to predict pharmacokinetic profiles.		(Kuepfer et al., 2016; Niederalt et al., 2018; Zhang et al., 2025b; Mi et al., 2025)

modelling how stable these contaminant-target complexes are and how they behave over time (Salo-Ahen et al., 2020). To measure how tightly they bind, methods like MM/PBSA calculate binding free energy, giving solid way for better risk assessment (Chen et al., 2018). Additionally, physiologically based pharmacokinetic (PBPK) modeling predicts how contaminants are absorbed, distributed, metabolized, and excreted (ADME) in the body (Sharma et al., 2018). This allows for thorough risk assessments without needing animal tests. A schematic of the computational risk assessment paradigm for food contaminants is presented in Figure 1. The graphic integrates the initial exposure *via* foodstuffs with the subsequent multi-scale modeling approach from atomistic simulations to population-level tools. To provide a comprehensive overview of the computational approaches employed in modern risk assessment, we have compiled a list of representative software tools in Table 1. This table lists commonly used applications, categorizing them by their primary function in the workflow, including molecular docking, molecular dynamics simulations, binding energy calculations, and physiologically based pharmacokinetic (PBPK) modeling. Tools for regulatory-oriented tasks, such as the OECD QSAR Toolbox, and for systems-level analysis, like network analysis software are also included. This compilation serves to contextualize the diverse toolkit available to researchers and frames the methodological landscape within which our subsequent analysis is situated. A critical awareness of each method's predictive value and limitations, validated where possible with experimental evidence, supports their effective application in food safety.

4.1 Molecular docking and virtual screening

Molecular docking is a powerful computational technique used to predict interactions between a ligand and its receptor (Vidal-

Limon et al., 2022; Okus et al., 2024). It estimates the binding energy of a ligand with a receptor and helps to understand the strength and nature of their interaction. In contrast, virtual screening allows the simultaneous evaluation of multiple ligands or ligand database with a receptor, making it valuable for identifying potential lead compounds (Agnihotry et al., 2020; Pathak et al., 2020). While molecular docking has traditionally been applied in drug discovery research, it is now frequently used in the field of toxicology to assess health risks by predicting how toxins may interact with human receptors (Zhao et al., 2025). In recent years, molecular docking and virtual screening has emerged as a transformative computational tool for elucidating interactions between food contaminants such as nanoparticles and chemical toxins with biological targets. This approach accelerates risk assessment by predicting molecular interactions and prioritizing toxic compounds based on their binding free energy for downstream analysis (Kar et al., 2024; Chu and Zi, 2024). Chu and Zi used molecular docking and network toxicology approaches to identify six core protein targets such as Serine/Threonine Kinase 1 (AKT1), Epidermal growth factor receptor (EGFR), Proto-oncogene tyrosine-protein kinase Src (SRC), Tumor necrosis factor (TNF), Caspase-3 (CASP3), Apoptosis regulator Bcl-2 (BCL2). Aflatoxin B_1 (AFB_1) strongly interact these proteins with binding energies < −7.5 kcal mol^{-1}, confirming their role in liver injury. This docking-based investigations revealed AFB_1's disruption of apoptosis pathways enabling rapid, animal-free toxicity risk assessment for food contaminants (Chu and Zi, 2024). Additionally, the possible interactions and toxicity of nanoparticles such as CuO, TiO_2, ZnO, Mn_2O_3, Fe_3O_4, Au, Ag, and Fe3O4 with biological targets have also been evaluated using molecular docking (Abdelsattar et al., 2021; Forest, 2022). The reliability of molecular docking predictions is quantitatively assessed using several validation metrics. The root-mean-square deviation (RMSD) is the standard for evaluating pose prediction accuracy; an RMSD of less than 2.0 Å from an experimentally determined co-crystal structure is often considered a successful docking run (Ding et al., 2016). Molecular primarily excels with small, drug-like molecules, but its application to nanoparticles or other non-traditional ligands is often not feasible. The size and multi-point binding modes of nanoparticles fall outside the scope of standard docking algorithms and scoring functions, which are parameterized for atomic-level interactions (Abughalia et al., 2025). Additionally, the accuracy of scoring functions remains a bottleneck, as they can struggle to correctly rank compounds due to approximations in modeling solvation and entropic effects. Recognizing these constraints is crucial for the appropriate application and interpretation of docking studies.

4.2 Molecular dynamics simulations and MM-PBSA

MD Simulations use Newton's mechanics to describe the nuclear motions. Treating atoms and molecules as classical particles gives valuable information about thermodynamics, structures and dynamical properties of the condensed matter from pure liquids to complex biomolecular systems. Molecular dynamics simulations compute motions, so it makes possible to describe position, velocities and changes *versus* time of individual molecules in solids, liquids o gases. With the use of MD simulations coupled with DFTB(DFTB+ simulation package — https://dftbplus.org/index.html), which can incorporate quasi-electronic structure calculations, it may include direct interactions with water and reactivity (Figure 2), we can go a step further in the field of toxicology and calculate physical and chemical properties that can be subsequently used as descriptors (Escorihuela Martí, 2019).

MD simulations play a significant role in structural bioinformatics by helping to understand the behaviour of macromolecules such as proteins and nucleic acids, and how ligands interact with their receptors (Hollingsworth and Dror, 2018; Singh et al., 2018). In food science, MD simulations is a useful technique for studying food processing at the molecular level. It helps optimize flavour and contributes to the development of higher-quality, more functional, nutritionally rich and safer food products (Singh et al., 2018; Smith et al., 2022). Additionally, Molecular Mechanics-Poisson–Boltzmann Surface Area (MM-PBSA) helps utilize trajectory data obtained from MDS to estimate the binding free energy of toxic chemicals with target receptors. Therefore, MDS and MM/PBSA are highly valuable tools for the computational assessment of contaminants present in food (Wang et al., 2018; Jin and Wei, 2024). Bisphenol analogs are frequently detected in food products (Andújar et al., 2019). A recent study demonstrated their interaction with estrogen receptor alpha (ERα). For instance, MDS showed that BPA analogs induce distinct conformational changes in the ligand-binding domain of ERα compared to BPA so that it can be alter its normal behaviour. The findings suggest that computational methods may serve as a reliable approach to assess androgenic and estrogenic activity in materials that come into contact with food (Cavaliere et al., 2020).

To bridge the computational results with toxicological outcomes, the binding free energies (ΔGbind) calculated *via* MM/PBSA provide a quantitative measure of ligand-receptor complex stability. A more negative ΔGbind signifies a more stable interaction, which often correlates with a stronger biological effect (Zare et al., 2024). For example, a high binding affinity for a toxicant towards a key protein, can directly predict the potential for acute toxicity by inhibiting its function (Liu S. et al., 2024; Chalaris et al., 2025). Furthermore, beyond specific protein targets, the principles of molecular interactions explored in these simulations are fundamental for predicting broader ADMET properties. The same forces governing protein-ligand binding also influence a molecule's passive membrane permeability and bioavailability, key determinants for its absorption and distribution within an organism (Gomes et al., 2023).

4.3 QSAR and machine learning models

QSAR (Quantitative Structure-Activity Relationship) (Pradeep et al., 2020; Gajewicz et al., 2015) and machine learning (ML) models (Seal et al., 2025; Hong, 2023) are revolutionizing food toxicology and helps in rapid, cost-effective and predictive assessments of chemical hazards (Pradeep et al., 2020). QSAR and ML are changing how we handle food safety. Instead of waiting to test for toxins after they have caused harm, these tools let us predict risks in advance (Pradeep et al., 2020; Wu et al., 2024). By analyzing a

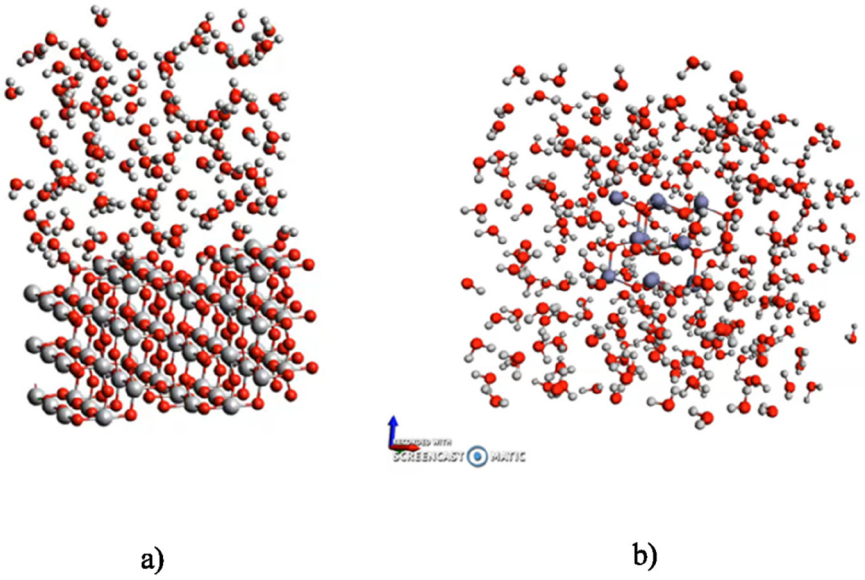

FIGURE 2
(a) 3 × 3 × 2 TiO_2 slab, exposing the (100) surface. **(b)** 3 × 3 × 2 TiO_2 nanoparticle, exposing the (100) surface with 108 molecules of water that represent a water density of ~1 g cm^{-3} in the region of periodic images (Escorihuela Martí, 2019).

chemical's structure, applying smart algorithms, and making models easier to interpret, we can quickly flag hazards from microplastics to drug residues in food products (Pradeep et al., 2020; Wu et al., 2024; Yang et al., 2023): The challenges like inconsistent data quality or global regulatory gaps still need teamwork to solve (Bo et al., 2023). Additionally, combining multi-omics data help us stop food toxicity threats before they even emerge (Su et al., 2024; Son et al., 2024). As recent studies show, these methods are becoming vital for initial risk assessments where traditional data is limited, truly reshaping food safety for the future (Honma et al., 2019; Pradeep et al., 2020). Using high-throughput QSAR modelling, researchers screened over 3,000 food-related compounds, ultimately identifying 160 as priority endocrine-disrupting hazards (Yang et al., 2023). Additionally, researchers developed novel QSAR models using cancer-relevant PubChem bioassays and multi-algorithm ML for predicting carcinogenicity. The models successfully prioritized 342 chemicals and identified new potential human carcinogens validated by literature (Chung et al., 2023).

To address key challenges in applying ML approaches to toxicology, we can focus on three critical areas such as adopting standardized characterization protocols to ensure data quality; developing descriptors grounded in mechanistic toxicology to improve interpretability; and finally, aligning entire workflow with OECD-accepted QSAR validation principles for regulatory acceptance (OECD QSAR Toolbox|https://www.oecd.org/en/data/tools/oecd-qsar-toolbox.html).

4.4 Network toxicology and pathway analysis

Network and pathway analysis is the key approach that help to visualize the clear picture of biological system. In toxicology, network analysis maps out how toxins engage with the cell's molecular machinery (Jin et al., 2025), while pathway analysis reveals which cellular processes go off course (Wiklund et al., 2023). By combining these approaches, we can turn complex omics datasets into clear, mechanism-driven insights for assessing food safety paving the way for more precise and predictive evaluations (Zhang S. et al., 2024). Li *et al.* used network toxicology to identify 93 shared molecular targets associated with BPA-induced diabetic cardiomyopathy and related pathways. The study highlights the importance of evaluating BPA substitutes and provides insights to inform regulatory limits on food-contact materials (Li et al., 2025). Lei *et al.* utilized network toxicology to identified 22 core targets from 259 tetracycline targets, revealing mechanisms such as affecting PI3K-Akt/MAPK that justify reevaluating antibiotic residues in food for risk mitigation (Lei et al., 2024; Lei et al., 2024; Lei et al., 2024; Lei et al., 2024).

This network-based approach provides crucial context for molecular-level findings. While docking and QSAR predict specific protein-ligand interactions, network toxicology elucidates the broader biological consequences, showing how a predicted binding event may propagate through a pathway to ultimately evidence as toxicity (Valls-Margarit et al., 2023; Barel and Herwig, 2018).

4.5 Physiologically based pharmacokinetic (PBPK) models

Physiologically based pharmacokinetic (PBPK) modeling is a powerful predictive toxicology tool that uses a mechanistic framework to describe absorption, distribution, metabolism, and excretion (ADME) of food-borne chemicals (Mi and Lin, 2025; Lipscomb et al., 2012). This approach allows for the estimation of

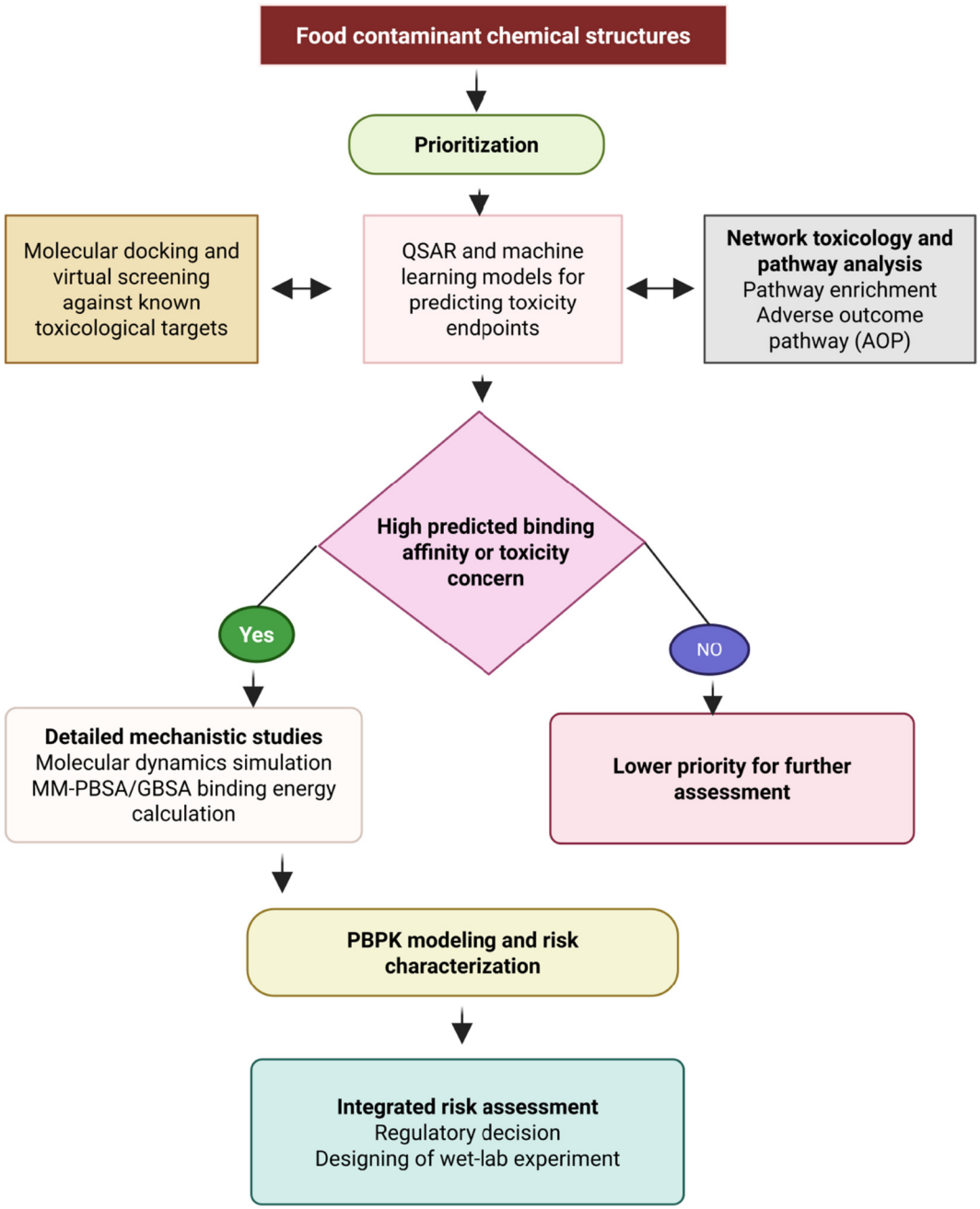

FIGURE 3
Workflow for computational risk assessment of food contaminants. The pipeline integrates *in silico* methods for hazard prioritization with PBPK modeling. The outcome directs resources toward high-risk compounds for advanced simulation, supporting efficient risk management and hypothesis-driven wet-lab validation.

chemical concentrations in human tissues, making it possible to accurately extrapolate data across different species and doses. By accounting for real-world exposure scenarios, PBPK models help to reduce the need for animal testing, inform regulatory decisions, and enhance risk assessments for food contaminants and residues (Lipscomb et al., 2012; Deepika and Kumar, 2023). PBPK models are also key t for predicting food-drug interactions, determining how meals can alter drugs' behaviours (Riedmaier et al., 2020). For instance, Dede *et al.* used PBPK models to assess human exposure to toxic elements (As, Cd, Cr, Ni, Pb) from home-grown produce. The approach enhances biomonitoring accuracy, supporting human health risk assessment in environmental exposure studies (Riedmaier et al., 2020). Riedmaier *et al.* evaluated PBPK model 's ability to predict how food affects the absorption of orally administered drugs using data from 30 compounds. By applying a systematic modeling approach, high to moderate prediction confidence was achieved for most compounds (Riedmaier et al., 2020). Given their importance, several PBPK models have been developed to specifically assess food toxicity and support risk assessment (Li et al., 2017; Ai et al., 2024; Tistaert et al., 2019).

Therefore, "*in silico*" approaches have strong potential to elucidate the nature of toxicants in food, and the interconnections between these techniques in supporting risk assessment. Figure 3 depicts an integrative workflow for food contaminant risk assessment, illustrating a pipeline that interconnects computational approaches from chemical structures to system-level prediction. This synergy enhances the robustness of both toxin prioritization and the overall assessment, thereby strengthening the foundation for regulatory decisions.

To further strengthen the applicability of our discussion, we highlight the growing use of PBPK modeling in the risk assessment of food contaminants and animal-derived products. These models are pivotal for predicting tissue residue depletion and establishing extralabel withdrawal intervals for veterinary drugs in food animals, directly ensuring the safety of products like meat, milk, and eggs (Lin et al., 2025). Furthermore, recent advancements are increasingly focused on refining these models to account for human physiological variability using probabilistic methods and Monte Carlo simulations, which provide a more robust estimation of human equivalent doses across diverse populations (Chou and Lin, 2023; Schacht et al., 2024). Finally, the field is being transformed by the integration of machine learning (ML) with PBPK modeling. ML approaches can now predict critical absorption, distribution, metabolism, and excretion (ADME) parameters directly from chemical structure, accelerating the development of robust models for a large number of compounds, even with limited experimental data (Chou and Lin, 2023; Mavroudis et al., 2023). This synergy between mechanistic modeling and data-driven prediction represents a powerful paradigm for high-throughput exposure and risk assessment.

5 Experimental validation of computational findings

Computational prediction significantly saves time and funds, enabling the rapid toxicological evaluation of food contaminants. Computational approaches are helpful in prioritizing hazardous contaminants and elucidating their mechanisms of toxic action. However, verifying these computational predictions necessitates rigorous experimental validation. This review discusses integrated computational methodologies, such as molecular docking, molecular dynamics simulations and binding energy calculations, which are used to visualize and predict the interactions between contaminants and human receptors. Experimental techniques, including bioluminescence resonance energy transfer (BRET)-based assays and Western blotting, are employed to understand the subsequent toxic effects (Jeong et al., 2025a; Jeong et al., 2025b). Furthermore, data from *in vivo* animal pharmacokinetic studies are crucial for validating PBPK models (Jobst et al., 2025). A recent study employed molecular docking and molecular dynamics to predict interactions of various benzophenones with the androgen receptor, identifying key amino acid residues and binding affinities. These computational predictions were subsequently validated using BRET-based, luciferase assays and Western blot, which showed good agreement and thereby supported the credibility of the computational approach (Jeong et al., 2025a). Jeong et al. (2025b) combined molecular docking and molecular dynamics simulations to explore how methiocarb interacts with estrogen receptor alpha (ERα), revealing key binding residues and predicted binding strengths. These computational insights were confirmed through *in vitro* experiments, demonstrating that methiocarb activates ERα and validating the predictive power of the computational approach (Jeong et al., 2025b). Duan et al. (2025a) utilized a combination of network toxicology and molecular docking to identify 49 common targets linking acrylamide (ACR) exposure to breast cancer (BC). Key genes, including EGFR, FN1, JUN, and COL1A1, were further validated through molecular dynamics simulations, which confirmed binding stability, and immunohistochemistry, which demonstrated their altered expression in tissues. These results suggest a potential mechanistic role for ACR in BC development (Duan et al., 2025a). A study adapted an existing PBPK model to simulate the pharmacokinetics of PFOS and PFOA. The model was validated by comparing its predictions to experimentally measured human data, successfully demonstrating its utility for real-world risk assessment applications (Fàbrega et al., 2014). Therefore, the strong correlation between these computational and experimental approaches not only supports the predictive power of the models but also provides a robust, mechanistically up-to-date foundation for developing targeted mitigation strategies against food contaminants to support health risk assessments.

6 Risk assessment and regulatory frameworks

Food regulations are built on a framework that first identifies and assesses hazards, then establishes maximum levels for contaminants, determines their toxicity, monitors products to ensure compliance, and finally evaluates the overall public health impact.

For engineered nanomaterials (ENMs) in food, risk assessment involves evaluating potential hazards and exposures to determine the likelihood and severity of adverse health effects. This process must account for the unique properties of ENMs, their interactions with the body, and potential exposure routes through food. A tiered approach, combining "*in silico*", "*in vitro*", and "*in vivo*" studies, is often used to assess ENM safety (Usmani et al., 2024).

Regulatory bodies like the European Food Safety Authority (EFSA) and the U.S. Food and Drug Administration (FDA) play a critical role in this process. EFSA, for example, evaluates the safety of chemicals that could harm humans, animals, or the environment. It has created the OpenFoodTox 2.0 database, an open-source resource detailing critical toxicological endpoints for various substances under European legislation. The FDA identifies and assesses the most significant toxins in food, while the World Health Organization (WHO) works to establish international food safety standards.

Significant efforts have been made to develop specific guidelines for these assessments. In 2011, EFSA published its *Guidance on the risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain* (Committee et al., 2011). This was followed in 2021 by updated guidance that specifically addressed human and animal health risks. These guidelines emphasize that testing nanomaterials requires consideration of their unique morphological and chemical characteristics, which can alter their biokinetic behavior and toxicological responses compared to their non-nano counterparts. Therefore, applicants must conduct a separate physicochemical characterization and specific risk assessment for each distinct nanomaterial.

In a move towards modernizing risk assessment, EFSA's Strategy 2027 advocates for the promotion of New Approach Methodologies (NAMs). These methods, based on alternatives to animal experiments, aim to develop cutting-edge techniques and improve the quality and efficiency of hazard risk assessment for chemicals and food-related substances (EFSA Strategy 2027 – Science, safe food, sustainability|EFSA, n. d.)

7 Mitigation strategies

Multiple evidence-based approaches exist to mitigate food contamination, including agricultural controls (El Kayal et al., 2024; Periasamy and Gopi, 2023), advanced food processing technologies (Hassan and Zhou, 2018) biological detoxification methods using microbes as well as enzymes and enforced regulatory measures (Hassan and Zhou, 2018). Collectively, these strategies reduce toxin risks to ensure safer food supplies and protect human and environmental health (El Kayal et al., 2024). Onyeaka *et al.* highlight the growing concern of chemical contaminants in food, their sources, and the associated health risks. They emphasize stronger regulations, surveillance, and global best practices to minimize contamination and protect public health, especially in developing nations (Onyeaka et al., 2024).

Agricultural practices are considered the first line of defense in preventing food contamination before it reaches us. Good agricultural practices help minimize biological and chemical hazards, but they require the use of clean irrigation water, healthy soil management, and avoiding harmful chemical pesticides. On the animal food side, it is important to maintain animal health through proper vaccinations and ensure that animal feed is free from contaminants. Training farmers is also essential to support these practices (Lepper et al., 2017). Advanced food processing approaches such as Pulsed Electric Fields (PEF) (Ghoshal, 2023), High Pressure Processing (HPP) (Koutsoumanis et al., 2022), and Cold Plasma (Harikrishna et al., 2023) play a significant role in reducing contaminants and inactivating pathogens in food products. Therefore, these technologies hold immense potential to be employed more frequently for mitigating toxins in food (Nunes et al., 2021).

Biological detoxification using microbes such as lactic acid bacteria (Średnicka et al., 2021; Muhialdin et al., 2020) and enzymes like laccases, reductases, oxidases, and peroxidases (Liu M. et al., 2024) helps to degrade and transform contaminants such as mycotoxins, pesticides, and allergens. These methods provide targeted, eco-friendly alternatives to chemical treatments, enhancing food safety by mitigating harmful substances (Abraham et al., 2022; Średnicka et al., 2021; Karlovsky et al., 2016).

Additionally, regulatory measures play a crucial role in the mitigation of contaminants in food (Food Chemical Safety|FDA, 2025), (Yu, 2024), Regional comparisons of regulatory systems reveal distinct differences shaped by variations in resources, infrastructure, and enforcement capacity (Duan et al., 2025a). Therefore, international, regional, and national regulatory frameworks can help to establish multilayered controls to mitigate food contamination risks and protect consumers globally (Duan et al., 2025b). Predictive modeling supports mitigation efforts by enabling the *in silico* design of safer materials, such as simulating polymer coatings to minimize nanoparticle release. QSAR models can proactively identify structural features that contribute to toxicity, helping researchers design or select chemical alternatives with reduced environmental impact (Shan et al., 2024).

The standardisation of the experimental tests is required to validate the results of modelling studies. It is necessary that this standardisation works together with computational and experimental methodologies to gain future insight into risk assessment and other challenges. For instance, the database https://data.enanomapper.net/ where many projects from European Union have been introduced their experimental data of toxicity characterisation for risk assessment. The use of *in silico* methods and advanced machine learning techniques to obtain NP descriptors reals for experimental comparison may become the next standard procedure to accelerate the evaluation of toxicity.

8 Conclusion

This review has elucidated the critical role of computational methods in analyzing the toxicity mechanisms of food contaminants. The advancing age of techniques like molecular docking, MD simulations, QSAR, and PBPK modeling now positions them for robust use in regulatory screening and prioritization. However, critical gaps remain. For nanoparticles, these include a shortage of high-quality reference data for model validation and the limited development of nanomaterial-specific models. The most promising frontier lies in the planned integration of machine learning with established mechanistic models, building hybrid frameworks that are both predictive and interpretable. This evolving computational toolkit is the foundation of a practical "safety-by-design" paradigm, enabling the proactive identification of hazards before products enter the market. To realize this potential, a intensive effort towards international harmonization of regulatory standards is essential. Through supporting these advanced, ethical tools, we can not only safeguard the global food supply but also foster responsible innovation, ensuring that public health protection keeps pace with technological advancement.

Author contributions

LE: Supervision, Writing – review and editing, Conceptualization, Funding acquisition, Writing – original draft. RP: Validation, Conceptualization, Writing – review and editing, Writing – original draft. BM: Writing – review and editing, Validation, Supervision, Writing – original draft. VK: Supervision, Writing – review and editing, Writing – original draft.

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