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Applications and toxicological issues surrounding nanotechnology in the food industry*

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Abstract: With the rapid development of nanotechnology, the presence of nanoparticles (NPs) in commercially available products is becoming more and more common. The field of food nanotechnology has experienced significant growth over the last five years. Agricultural cultivation, food processing, food packaging, food security, and water purification are examples of the important sectors linked with nanotechnology in the food production chain. However, safety concerns about such nanotechnology and the use of nanomaterials are increasing. Many determinants for the unusual activities and toxicities of the nanomaterials involving particle size, chemical composition, surface structure, and dosage are considered as well as three main exposure routes, including inhalation, ingestion, and dermal exposure. In addition, the trends and progress for toxicity and risk evaluation of the nanomaterials used in the food industry are also reviewed, which are helpful to understand and establish a regulatory system for the further development and use of NPs in the food industry.

Keywords: food industry; nanomaterials; nanotechnology; nanotoxicology; risk assessment.

INTRODUCTION

The emergence of nanotechnology greatly influences almost every field of modern technological development, such as computer electronics, communication, energy production, and medicine [1]. The food industry is no exception, either. With this rapid development of nanotechnology, the presence of nanoparticles (NPs) in commercially available products is becoming more and more common. The field of food nanotechnology has experienced significant growth over the last five years. Agricultural cultivation, food processing, food packaging, food security, and water purification are examples of important areas in the food production chain that are being influenced by nanotechnology. This novel technology offers scope to increase food productivity and to supply fresher and healthier foodstuffs, which are especially important needs for consumers in developing countries. Furthermore, it is possible to enhance the utilization of nutrition and nutraceuticals with the aid of nanodelivery systems (NDSs). However, the novel properties of the nanomaterials may also endow themselves side effects different from the bulks on the environment, even on human beings [2]. Before nanotechnology can confidently be applied in consumer society, it is therefore imperative to identify and understand possible toxicological implications and detailed mechanisms of action of relevant nanomaterials. Since nanotechnology, especially in the food industry, is an emerging field, the question of "how to regulate food nano-

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technology to ensure that it develops in a scientific way" is a critical issue to resolve. However, there are no suitable regulatory frameworks at present to address this issue. In this review, we will focus on a range of relevant topics related to nanotechnology in the food industry.

APPLICATIONS OF NANOTECHNOLOGY IN THE FOOD INDUSTRY

Just as the advent of genetically modified organisms (GMOs) profoundly influenced perceptions of biotechnology, so has the emergence of "nanofood" or "ultrafood" as an outcome of the rapid development of nanotechnology in the food industry. However, it is difficult to distinguish which products can be called nanofood. Joseph and Morrison [3] point out that "The definition of nanofood is that nanotechnology techniques or tools are used during cultivation, production, processing, or packaging of the food." In fact, many natural NPs or nanomaterials, such as the proteins, polysaccharides, and lipids, existed before the appearance of nanotechnology. The sizes of these materials are all in the range of 10–100 nm in one dimension at least. Those natural NPs in use as food-grade materials are generally recognized as safe (GRAS). Therefore, we only refer to the engineered or anthropogenic nanomaterials in this review. In this section, we will discuss the applications of nanotechnology in the food industry and related fields, such as agricultural cultivation, food processing, food packaging, food security, and water purification.

Agricultural cultivation

Increasing crop yields has always been the primary goal of the world's subsistence farmers, especially in developing countries. This goal can be realized through several strategies, including improving drought resistance, lodging resistance of crops, and nutritional availability. Methods for reducing pest attacks are also effective and desirable. It has been reported that the use of pesticide and herbicide can reduce grain loss by 30–40 %. Genetic engineering techniques have played critical roles in increasing production of the crop. The emergence of nanotechnology offers great promise in further addressing these areas. Early approaches to pest control relied heavily on chemical pesticides as the main agents of extermination. However, the highly negative effects of chemical pesticides on the environment and the human body are well documented. Some of these agents are carcinogens, and many insecticide residues persist in soil and water for long periods, thereby greatly increasing the danger of human and animal contact and exposure. Public awareness of these health hazards has grown in modern times. One of the worst consequences of pesticide misuse has been the proliferation of a number of resistant insects. Some additional factors that detract from conventional use and efficacy of pesticides include wind, sunlight, and rain, which often necessitate repeated periodic administration to achieve their purpose. This, in turn, exacerbates the problem of overuse of pesticides and consequential cumulative effects on the environment. A desirable option is to protect the active ingredients from degradation and maintain their efficacy for more protracted periods. How can this be achieved? The emergence of nanotechnology offers potential to solve problems of pesticide delivery and persistence without the foregoing negative effects on the environment. As a result of their small size, nanomaterials have some novel properties that differ from the bulks with identical components [4]. When dispersed into smaller particles (1–100 nm), the active ingredients will spread on the leaf surfaces uniformly and be internalized by chewing insects [5]. Controlled release of chemical pesticide has been studied in recent years, such as avermectin encapsulated into the porous hollow Si NPs [6] and the polymeric NP formulation of bifenthrin [7]. Insect pests prevent water loss by using a variety of cuticular lipids. While Si NP is absorbed into the cuticular lipid by physical adsorption, the pest will be killed. Meanwhile, the application of NPs will not impact the photosynthesis or respiration of the crop and the gene expression in insect trachea [8]. Then, fewer resistant insects exist for pesticides. Micro- or nanoemulsion is another novel carrier for the drug and pesticide delivery. Microemulsion can improve the solubility and bioavailability, minimize the negative effects, and control the release of the drug [9]. With its advantages of high kinetic stability, small droplet size, low viscosity, and optical transparency, nanoemulsion is fascinating in agrochemicals for pesticide delivery [10] and other industrial applications [11–14]. Many micro- or nanoemulsion formulations of pesticides have been developed, e.g., β-cypermethrin nanosuspension [15]. In brief, nanocarriers broaden the application for the chemical pesticide in agriculture.

Food processing

Currently, people are exploring every possibility of processing food for enjoying and making good use of the nutrients. Life organisms are a mixture of many sophisticated systems. From the oral cavity to the intestines, each system has its own intrinsic environment. In other words, there are a number of factors affecting the absorption of food. Meanwhile, the organism needs large quantities of different nutrients such as vitamins, fatty acids, and proteins. During the course of absorption, some nutrients will be degraded before entering into the target site of the body. Then, the nutrients will be assimilated at low bioavailability. For instance, vitamin A is susceptible to oxidation and isomerization. Its deficiency influences the development of children because of its key roles in vision and ocular health, immune system development, and neurological function [16]. Various technologies for protecting vitamin A have been developed, including the emulsion systems, solid lipid nanoparticles (SLNs), and polymer encapsulation [17]. This NDS is helpful for resolving these problems. It can deliver the nutrients efficiently to cells, without affecting the color or taste of the food. The functional food ingredients can be also delivered to the target site by NDS [18,19]. In general, the NP vehicles are prepared by two approaches of "top-down" and "bottom-up" [20–25]. Taepaiboon et al. [26] prepared electrospun cellulose acetate nanofiber of vitamin A acid and vitamin E as transdermal and dermal therapeutic agents.

Novel functional foods may have physiological benefits or reduce the risks of some diseases. However, some functional components, such as proteins and peptides, are highly susceptible to enzymatic degradation in the gastrointestinal (GI) tract, which leads to poor absorption. Nanotechnology may provide solutions to these challenges [27–29]. Novel controlled delivery systems can overcome these limitations and increase patient compliance. The NPs can significantly prolong the residence time of the compound in the GI tract [30–33] and enter into the deep tissues easily [34–37]. Then it will release the active ingredients at the right place and the right time. Graf [38] synthesized the poly(alkylcyanoacrylate) (PACA) NP for delivery of proteins and peptides with the microemulsion serving as the template. Polymers directly extracted or removed from biomass (i.e., polysaccharides, proteins, polypeptides, and polynucleotides) are optimal materials for the NDS. For instance, chitosan is a nontoxic, biocompatible, biodegradable, and less expensive byproduct of the seafood industry [39–44], and some of its derivatives can self-assemble to form NPs. Zhang et al. [45] investigated the synthesis of chitosan-derived nanomicelles for controlled release and targeted delivery of hydrophobic bioactive food factors. Some proteins are able to form gel and emulsion, and then they can be ideal materials for the encapsulation of bioactive compounds [33]. The nanotube made from the hydrolysis of milk α-lactalbumin can be applied in food and pharmaceutics [46]. The smart delivery system, which combines the NDS with the nanosensor, will be the most ideal nutrition delivery system. It will release the ingredients until the nanosensor detects the deficiency of the specific component. However, it is almost impossible to design effective NDSs without completely understanding the biological processes that regulate uptake and bioavailability. E. Acosta [47] summarized the mechanisms of active ingredient uptake through oral exposure using NP systems (Fig. 1).

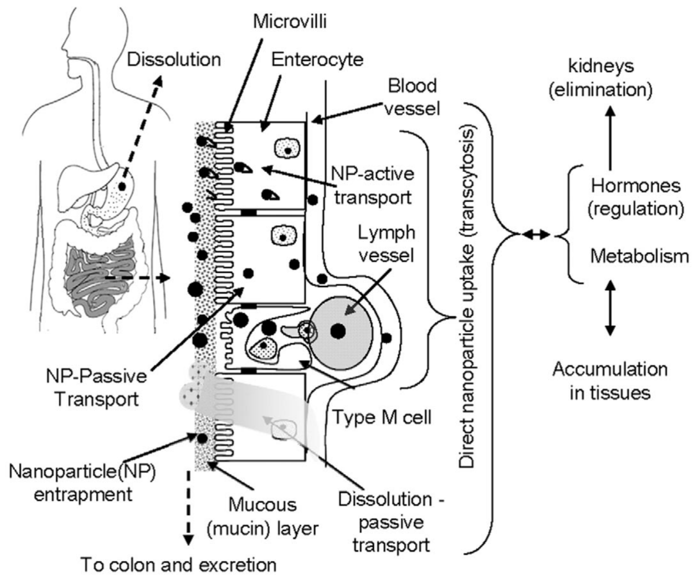

Fig. 1 Schematic of the mechanisms of active ingredient uptake through oral exposure using NP systems (reprinted with permission from ref. [47], copyright © 2009 Elsevier).

The extraction of nutrient ingredients from raw materials is an integral part of the food industry. Meanwhile, an effective and efficient extraction process is also very important. However, it is never enough to optimize the manufacturing technique and the monitoring method. With the rapid development of technology, conventional methods for food processing will be substituted gradually by other novel techniques. There is no doubt that nanoscience and -technology will play important roles during this innovation. With the help of nanotechnology, people will be getting to know how to select the optimal raw materials and improve the processing rationally. For example, inulin is a fructan carbohydrate and the source for the production of fructose [48]. It is an ingredient of dietetic and children's foods. Hence, developing a novel method for the determination of inulin is of great interest for monitoring the extraction and the production of fructose. Javier Manso and his colleagues [49] co-immobilized the fructose dehydrogenase (FDH) and the inulinase (INU) on the modified Au NP as a biosensor to determine the ingredient. This technique provided a rapid, stable, and high-sensitivity analytical method, which is attractive and promising compared with other complex and time-consuming methods. Furthermore, this technique can be also applied to other carbohydrates.

Food processing involves a wide variety of raw materials, high biosafety requirements, and well-regulated technological processes. An ideal delivery system must own at least four characteristics such as targeted delivery, protecting the ingredient from degradation, controlled release, and compatibility with the system [50], which means that the encapsulating matrices should be GRAS. The NDS or smart delivery system is currently in its earlier stage. When enjoying the benefits of the NDS, the regulation should not be understated.

Food packaging

The quality of life becomes the focus. For example, people become concerned about the freshness and the taste of food. Then, a challenge arises of how to preserve food, which leads to the appearance of food packaging. The development for packaging materials can be classified into three phases. The first phase consists of conventional packaging with undegradable composites. The second phase consists of green and biodegradable polymer materials. The last phase consists of "active and intelligent packaging" with nanocomposites and -sensors.

Food packaging provides the mechanical support for non-solid food and protects it from external influences such as microorganisms, oxygen, off-odors, light, and so on. Food packaging guarantees convenience in food handling and preserves the food for an extended shelf-life. In the beginning, plastics were the main materials used in food packaging due to their convenience and safety, low price, and good aesthetic qualities. These materials are generally made from polyolefins [e.g., polypropylene (PP), polyethylene (PE), polystyrene (PS), and poly(vinyl chloride) (PVC)], which are produced from fossil fuels [51]. However, these packaging materials are practically undegradable and will lead to serious environmental problems when discarded [52]. The critical issue for these conventional materials is that they must be inert to minimize the reaction between the packaging material and the food. In other words, it should extend the shelf-life of food while maintaining the food safety and quality.

Recently, because of environmental pollution, green polymer materials have become more desirable. The biodegradable and edible films from food-grade proteins, polysaccharides, and lipids have been explored as packaging materials [53–55]. Although they are environmentally friendly, these materials exhibit poor barrier and mechanical properties. These disadvantages include brittleness, low heat-distortion temperature, high gas permeability, low melting viscosity for further processing, and so on. Hence, these properties need to be improved in advance in order for them to substitute for traditional plastics [53,56]. Since nanomaterials have some unique properties significantly different from the bulks, nanotechnology may provide solutions to solve the above-mentioned challenges. Currently, the nanocomposites, which means the mixture of green biopolymers with inorganic nanomaterials, have received more attention than others. The inorganic nanomaterials serve as the nanoreinforcements for improving the practicability of biopolymers. Various nanomaterials have been developed, such as nanoclay (layered silicate) [57–61], cellulose nanowhiskers [62,63], ultrafine layered titanate [64], and carbon nanotubes (CNTs) [65–67]. After hybridization, the nanocomposites show unexpected mechanical properties, thermal stability [68], conductivity, and gas barrier properties [69], which will play critical roles in broadening the applications of the edible and biodegradable films [51,70] and resolving the problem of packaging waste [71,72]. Among them, the clay/polymer nanohybrids are the most commonly studied. When layered silicates are dispersed between polymeric chains, the fireproof, mechanical, and barrier properties are improved considerably and show good promise in the food industry [73–76]. The nanoclays had been developed to enhance the properties of zein nanobead or NP [77,78], thermoplastic starch [79], biopolyesters like polylactic acid (PLA) [80,81], and polyolefin films [82]. Meanwhile, the exfoliated NP completely dispersed between the polymeric chains shows better properties than that of the intercalated NP [82]. In addition, chitosan and tripolyphosphate NPs had been used to improve the mechanical and barrier properties of hydroxypropyl methylcellulose (HPMC) films significantly [83]. The tensile properties, thermal stability, and water vapor permeability were also reinforced by the NPs.

In traditional food packaging, the materials should be inert to ensure food safety. However, an innovational concept of "the active and intelligent packaging" occurs in packaging technology. The active packaging materials, including the moisture absorbers, oxygen absorbers, enzymes, antibacterial substances, and fungicides prolong the shelf-life and maintain or improve the packaging conditions. They can be classified into two types of non-migratory active and active releasing packaging [84]. The NPs of magnesium oxide, zinc oxide, and silver [85] with high antimicrobial ability are good examples. As for intelligent packaging, the intelligent materials or nanosensors are the ingredients that monitor the condition of packaged food or the environment surrounding the food [84]. It is attached as a label, incorporated into or printed on the packaging and provides detailed information throughout the supply chain [86], e.g., whether the quality is good or not. The nanosensors or "nano-electronic tongue" or "nano-nose" in the packaging can detect the food spoilage and pathogens within a short time, even minutes [87–89]. Then it will raise an alarm when the food is not safe to eat [90].

Food security

It goes without saying that food safety or security is of great importance to humans. There are great numbers of microorganisms surrounding us. The worse thing is that pathogens can modify their activities with the external environmental change [91]. For instance, vacuum technology made it possible to keep food for a long time at low temperature but also favored the growth of the bacterium to high levels, even leading to the emergence of new pathogens (e.g., *Yersinia enterocolitica* in the 1960s). Many foodborne pathogens result in the occurrence of related diseases. Then, the analytical method plays vital roles in the food security. However, traditional methods that are based on the growth of microorganisms require complicated sample handling and must be performed in microbiological labs. They also take a long time (several days). Later, according to the recognition between antibody and antigen, many methods were developed, including various enzyme-linked immunoabsorbent assays (ELISAs) [92] and immunomagnetic separation [93]. Since each bacterium has its specific genes, we can use the polymerase chain reaction (PCR) technologies, including regular, multiplex, real-time, and reverse transcriptase-PCRs, to detect foodborne pathogens [94–96]. Compared with culture-based methods, the PCRs are less time-consuming and high throughput. However, these methods still take several hours or overnight when detecting a few bacteria cell in the sample, which is expensive and inconvenient in the food industry. Owing to their unique physicochemical properties, nanomaterials show great promise and potential applications [97,98]. Then, the combination of nanomaterials and traditional detection methods may address these issues. Based on biorecognitions such as antibody–antigen recognition, adhesion-receptor recognition, antibiotic recognition, and complementary DNA sequence recognition, different kinds of biomolecules can be conjugated to nanomaterials to reduce the time for testing and to enhance sensitivity and portability. Various nanomaterials have been developed to detect foodborne pathogens and showed advantages compared to conventional methods (Table 1). Some of these nanomaterials [such as quantum dots (QDs), magnetic NPs, liposome, Si NPs, and Au NPs] only take hours or even several minutes to detect the microbe. In addition, the above nanomaterials can also be used for multipathogen detection. Meanwhile, these novel methods are more sensitive and simpler than traditional methods. The nickname of these functional nanomaterials is "nanosensor or nano-electronic tongue or nose". Nanocantilever is another kind of nanosensors and successfully used for detection in food and water [123,124]. It can detect the biological-binding interactions through the physical and electro-mechanical signals and recognize the pathogens [125,126]. These nanosensors also can be applied in detecting the drug residues and mercury contamination in food [127,128]. Sometimes, the hybridization of nanomaterials, e.g., the self-assembly of QDs and CNTs [129], could provide highly selective, ultrasensitive, fluorescence detection methods and have great potential in applications such as ultrasensitive pathogen DNA or antigen or antibody detection, molecular imaging, and photoelectrical biosensors.

Table 1 Advantages of nanomaterials used for food security.

Microorganisms or other pollutants	Nanomaterials	Advantages	References
E. coli O157:H7	Au NP	It binded to the antigen with high specificity and affinity and could be used as efficient labeling probe and multiligand carrier.	[99]
	Au nanowire	The nanowire could bind to the antibody with high affinity and detect the pathogen rapidly.	[100]
	Polymeric NP	It binded strongly with *E. coli* and had potential applications in the inhibition of enteropathogenic infections.	[101]
	Quantum dot	This method was rapid and simple and had potential applications for simultaneous detection of different bacterial species in a single sample. It took less than 1 h. And the detection limit was 10 CFU/ml.	[102,103]
	Carbon nanotube	With high polarizability and dielectrophoretic mobility, SWCNT could capture and detect low numbers of bacteria and submicron particles in milliliter-sized samples. Functionalized SWCNT provided even more specificity. For instance, the Gal-SWCNTs may be applied to other pathogens bearing galactose receptors.	[104–106]
	Magnetic NP	The sugar-coated magnetic NPs had potentials for fast bacterial detection and removal, which took less than 5 min and provided an attractive avenue for pathogen decontamination and diagnostic applications. It showed advantages in terms of higher capture efficiency, no need for mechanical mixing, and minimal sample preparation. The detection limit was 8 CFU/ml.	[107,108]
	Magnetic nanorice	With UVRR method, discriminative analysis to distinguish biomolecules or bacteria sorbed onto the immuno-nanorice could be done.	[109]
	Liposome	This assay did not need washing and incubation steps as in ELISAs and could be completed in 5 min. It had potential as a simple, rapid, and inexpensive test for quantitative screening of food samples for *E. coli* O157:H7 with densitometry.	[110,111]
	Carbon-magnetic nanotube	After conjugated with specific antibody, the BSA-MWCNT with encapsulated ferromagnetic elements captured the pathogen with high efficiency.	[112]
	Si NP	After conjugated with antibody, the NPs provided high fluorescent signals and could readily and specifically identify a variety of bacterium. It had great potentials in practical biotechnological and biomedical applications in various biodetection systems. It took less than 20 min. The detection limit was 1 CFU/g.	[113]

(*continues on next page*)

Table 1 (*Continued*).

Microorganisms or other pollutants	Nanomaterials	Advantages	References
L. monocytogenes	Polymeric NP	The antibody-coated NPs specifically recognized the antigen and generated higher intensity of fluorescent signals than the antibody alone did. This assay was more sensitive than the traditional assays.	[114]
	Quantum dot	The bioconjugated (dBSA) QDs had great potential for broad biological applications, such as fluorescence-based pathogen detection and in vitro or in vivo cell imaging. The detection limit was less than 100 cells.	[115]
	Magnetic NP	The optimized purification method showed a high specificity and sensitivity, with a detection level one log more sensitive than PCR carried out with nucleic acids obtained using commercial NPs. The detection limit was 10 CFU/ml.	[116,117]
	Liposome	Through the direct and competitive immunoassay tests, the protein G-liposomal nanovesicles were proved to be effective universal reagents for immunoassays and could detect several foodborne pathogens simultaneously. The detection limit was 1.5×10^4 CFU/ml.	[118]
S. aureus	Au NP	With specific antibody, the particle provided a rapid, convenient, highly sensitive, and specific detection method. It took less than 25 h. The detection limit was 10 CFU/g.	[119]
	Magnetic NP	Through combining FePt magnetic NPs with vancomycin, it provided a rapid and sensitive assay for detecting Gram-negative bacteria and might allow detection of other biological substrates at exceedingly low concentrations. It reduced the interference of protein and metabolite signals in the mass spectra of Gram-positive bacteria. It was very helpful to the MALDI-MS method. The detection limit was 8 CFU/ml.	[120,121]
	Si NP	With the multicolored FRET, this particle could detect multiple pathogens with high sensitivity. It took less than 30 min.	[122]
S. typhimurium	Quantum dot	The principle of this method could be extended to detect multiple species of bacteria (3–4 species) simultaneously. It took less than 2 h. The detection limit was 3.35×10^4 CFU/ml.	[103]
	Si NP	With the multicolored FRET, this particle could detect multiple pathogens with high sensitivity. It took less than 30 min.	[122]

Water purification

Water systems play critical roles in the food chain. Without clean water, which is free of toxic chemicals and pathogens, there will be no healthy body or even life for humans. Evidence showed that waterborne diseases were still the leading cause of death in many developing countries and at least one-sixth of the population did not have access to safe water [130]. A great number of factors bring serious challenges to the water system, such as various pathogens, industrial pollutants, agrochemicals, etc. Due to some reasons like extended droughts and population growth, the shortage of clean potable water is becoming more severe worldwide [131]. Hence, effective, low-cost, and safe water purification technologies are of great importance for resolving these problems. These purification technologies can be classified into two types, water disinfection and wastewater treatment.

For water disinfection, chemical disinfectants like free chlorine, chloramines, and ozone have played great roles in diminishing waterborne epidemics. However, increasing evidence demonstrates that there is a deadly limitation for chemical disinfectants. When chemical disinfectants are used in water, there will be the formation of disinfection byproducts (DBPs), most of which are carcinogens [132,133]. Meanwhile, some pathogens are resistant to chemical disinfectants. This requires a high dosage of disinfectants and will lead to more formation of DBPs. Then, there is an urgent need for novel disinfectants. Nanotechnology has generated innovations in many fields and may revolutionize water purification technology [134,135]. Some nanomaterials own antimicrobial activities, including chitosan [136], silver NPs (nAg) [137], photocatalytic TiO_2 [138,139], ZnO_2 NPs [140], fullerol [141], aqueous fullerene NPs (nC_{60}) [142], and CNTs [143]. One of the advantages of these materials is that they will not form DBPs. What is better is that some NPs like zero-valent iron (ZVI) NP can effectively eliminate the chlorine atoms and chlorine substituents and yield nontoxic byproducts [144–148]. Huang et al. [149] found that the reactivity depended strongly on the architectural features of the nanoreactor like the polyelectrolyte multilayer. Through regulating this nanoreactor, the active Fe NP can be fabricated. Wu et al. [150] investigated the activity of the Ni/Fe NPs. They show that the activity is enhanced after the hybridization, and the accumulation of the toxic byproducts is also reduced. Meanwhile, the nanomaterials can combine with the traditional disinfection technologies to realize an ideal effect. For instance, the UV disinfection effect can be enhanced by the TiO_2 NP [151,152]. However, there are some limitations for the nanomaterials, such as dispersion and sustainability of the antimicrobial activity. As we know, some NPs (e.g., TiO_2 and fullerene NPs) will aggregate in water or salt solutions [153]. Then, the activity will be diminished significantly. Sometimes, the NPs have antimicrobial ability under specific conditions. The chitosan shows antibacterial activity in acidic medium [154]. The retention of nanomaterials is another challenge when the nanomaterials escape from the treatment system. Meanwhile, the potential risk of the nanomaterials to human health should be considered.

Besides microoganisms, water systems can be contaminated by other pollutants such as heavy metals or the residues of pesticides and dyes released from the industry. These pollutants are hazardous to human health and the environment. Nanosorbents with unique properties provide great potential to remove the heavy metals efficiently and using cost-effective approaches. Liu et al. [155] reported that the coating magnetic NPs could remove the heavy metals efficiently. Some nanomaterials show unique photocatalytic properties such as TiO_2 NPs, Si NPs, and fullerene NPs, and have been developed to degrade dyes and pesticides in water systems [156–161].

DETERMINANTS OF ACTIVITIES AND TOXICITIES OF NANOMATERIALS IN THE FOOD INDUSTRY

As the size of nanomaterials decreases to 1–100 nm, the materials show some unique properties compared to the bulks [97,98], which determine the promising applications in almost all fields. Nel et al. [162] reviewed that the determinants of the activities and toxicities of nanomaterials included the size, chemical composition, surface structure, solubility, particle shape, and aggregation. The nanomaterials applied in the food industry, especially food processing and packaging, should be highly safe since humans can be exposed to these items directly. In this section, the in vivo and in vitro experiments of these determinants of NPs in the food industry will be reviewed.

Size

Size is the predominant factor for the unique properties of the NPs. As the size belongs to the range of 1–100 nm, the surface areas become significantly larger than those of the bulks. Evidence shows that the particle size, surface area, and surface properties are the important parameters in inducing the pulmonary response like inflammation [163,164]. After they have been deposited in the alveolar, the NPs may translocate to the distant organs such as the liver, kidney, spleen, and brain [165–170]. And there is optimal size for the uptake of the particle [171]. Borm et al. [172] found that there are higher lung tumor rates for ultrafine TiO_2 than that of fine TiO_2. Increasing evidence approved that the toxicities were size-dependent [173,174]. Höhr et al. [175] investigated the acute lung inflammatory response to modified fine and ultrafine TiO_2 in rats and reported that it is the surface area rather than the surface coating that determines the toxicity of the particles. However, Warheit et al. [176] compared the toxicity of the nanoscale TiO_2 nanorods and nanodots to the fine particles with identical compounds, which was against the hypothesis that the size and surface area were the determinants for the activity and toxicity of the nanomaterials. Recently, there was an interesting result that the particles (carbon black and TiO_2) at the concentration of 20 $\mu g/cm^2$ were cytotoxic to the renal cells but safe in vivo [177]. It means that the in vitro cellular systems should be developed so as to provide useful data for the toxicity study of the NPs. In addition to the side effects, the advantages of the nanomaterials should not be ignored. Some nanomaterials like TiO_2 can be recognized as "dangerous signals" by the immune system [178]. That is to say, some nanomaterials may be an important adjuvant for the immune system. The results also demonstrated that Crohn's disease would be more serious when reducing the dose of microscale TiO_2 in the diet for the patients [178].

Chemical compositions

The chemical compositions (purity, crystallinity, electronic properties, etc.) are also critical parameters for the nanomaterials. During the preparations of some nanomaterials like CNTs, there are usually some residues or impurities. Undoubtedly, these impurities may give rise to some health concerns of the materials and make it difficult to understand the inherent toxicity of the CNT [179]. The single-walled carbon nanotubes (SWCNTs) usually contain large amounts of iron, which can catalyze oxidative stress. That means iron-containing SWCNTs will be more toxic than iron-free SWCNTs. Murray et al. [180] also reported that SWCNT toxicity is dependent on the metal (particularly iron) content. The crystallinity also affects the activity and toxicity of the nanomaterials. For instance, TiO_2 has three kinds of crystallinity, anatase, rutile, and brookite. Evidence shows that the anatase TiO_2 NP shows stronger toxicity than that of the rutile [181]. Meanwhile, the anatase has stronger activity than the other two kinds of particles. Braydich-Stolle et al. [182] reported that 100 % anatase TiO_2 NPs, regardless of size, induce cell necrosis, while rutile initiates apoptosis through formation of reactive oxgen species (ROS).

Surface structure

The surface structure of NPs involves surface reactivity, surface groups, inorganic or organic coatings, etc. After being modified with these compounds, the biocompatibility, dispersion, or activity of NPs will be improved significantly. For instance, compared to bare NP, FeO_2 NP shows no toxicity to the cell when coated with poly(ethylene glycol) (PEG) [183]. Meanwhile, the surface charge of NPs will change with modifications. Then the activities and toxicities will change. Evidence [184] demonstrates that cationic surfaces are more toxic than anionic ones and the neutral surfaces are the most biocompatible. Villanueva et al. [185] investigated the internalization and biocompatibility of FeO_2 NP surface functionalized with four differently charged carbohydrates, which shows that there is high cellular uptake for cationic charged NP and no intracellular uptake for the neutral charged. The negative charged NP demonstrates a different uptake behavior depending on the nature of the coating. The mechanisms will be different from each other for NPs coated with different compounds. For instance, hydroxylated fullerene induces cell apoptosis independent of ROS generation while THF-nC_{60} causes cell necrosis via ROS [186]. QDs have numerous possible applications for in vivo imaging. Hence, the toxicological study of QDs is of great importance for humans. Geys et al. [187] investigated the acute toxicity and prothrombotic effects of QDs to mice. The study demonstrates that amine- and carboxyl-modified QDs at high doses cause significant vascular thrombosis in the pulmonary circulation, especially the latter. Auffan et al. [188] reviewed the effect of the chemical stability of metallic NPs on their cellular toxicity. They conclude that chemically stable metallic NPs have no significant cellular toxicity, whereas the NPs that are able to be oxidized, reduced, or dissolved are cytotoxic and even genotoxic for cellular organisms. TiO_2 NP is used in many applications and reported inert or safe to rats [189]. There was no difference in responses between the hydrophilic and -phobic NPs. Hence, the surface structure may play an important role in the toxicities of some specific nanomaterials.

Solubility

The solubility of the NPs also has great impact on the toxicity. Pott et al. [190] reported that the hydrophilic ultrafine TiO_2 is highly toxic and more lethal for rats than that of hydrophobic ultrafine TiO_2. The incidence of lung cancer would increase in the presence of some soluble Ni compounds [191]. Brunner et al. [192] found that solubility has a great effect on the cytotoxicity of NPs. When exposed to slightly soluble NPs like ZnO NP concentrations above 15 ppm, all MSTO or 3T3 cells died. But cells were not completely killed even at high exposure concentrations (30 ppm) of insoluble NPs. Meanwhile, some data shows that the surface coating or solubility may not be the determinant of the toxicity [175].

Aggregation

As is known to us, the functions are determined by the structures and the characteristics of the materials like proteins. In other words, we should understand all the characteristics and structures to uncover the functions of the materials completely. It is the same thing for nanomaterials, especially unveiling the negative effects. Limbach et al. [193] stated the importance of thorough nanomaterials characterization for the in vitro nanotoxicity studies. The nanotoxicological research is being done through in vivo and in vitro experiments. However, the detailed changes of the nanomaterials after entry into the cells are still unknown to us. For instance, it is unclear whether the particle size will increase or not within the system and how the aggregation of the particle affects the toxicity. Wick and his colleagues [194] reported that the agglomerates of the CNT gave rise to more pronounced cytotoxicity than the well-dispersed CNT and the control of asbestos. As a result, there has been evidence showing the importance of the aggregates in response to the particle [195,196]. Fullerene, another kind of carbon nanomaterial, has generated a great deal of interest because of its structural properties and chemical behavior. It has been well documented [197–200] that larger aggregation of aqueous fullerene would form when increasing the salinity or ionic strength of the aqueous media. Blickley and Mcclellan-Green [201] investigated the toxicity of aqueous fullerene aggregates in adult and larval *Fundulus heteroclitus*. Their study shows that aggregates of aqua-nC_{60} adheres to the chorion but does not affect development of the embryos or their hatching success. NPs in the dry state can be in two forms, including aggregated (hard bonds between primary particles) and agglomerated (held by weaker van der Waals forces). And agglomerated NP can be separated by overcoming the weaker attractive forces when dispersed in solution. A certain state of the particles should be selected depending on the objective of the toxicological studies. Jiang et al. [202] reported that they have developed a methodology to distinguish agglomerates from aggregates and estimated the extent of particle agglomeration. This will be very helpful for understanding the realistic toxicity of nanomaterials.

One point, which should not be ignored, is that nanotoxicity may not be determined by only one element. In other words, it is not accurate to determine which factor determines the activity or toxicity of nanomaterials. In addition to the above-mentioned characteristics, there are still other elements affecting the activities and toxicities of the nanomaterials. The route for uptake of the NP is one of these elements. It may demonstrate different effects through different routes. Li et al. [203] reported that it is the pH values in medium that play an important role in affecting the pulmonary toxicity of the TiO_2 NP rather than the particle size, surface area, and aggregation. Since there are so many determinants and factors affecting the activities and toxicities of the nanomaterials, the complete and scientific characterizations are significant for understanding and assessing the positive and negative effects of nanomaterials. Nanotechnology is revolutionizing the food industry and other related fields. Hence, it becomes more urgent than ever before, during these assessments, to identify the nanofood. Meanwhile, the dose metrics will be considerably helpful for the assessment. In a word, if we want to make full use of nanomaterials, we must understand them completely.

ROUTES FOR UPTAKE

Besides the characteristics determining the activity and toxicity of the nanomaterials, the exposure routes are also critical elements influencing the interactions between the nanomaterials and the tissues or cells. Generally speaking, humans can uptake nanomaterials through three main routes, including inhalation, ingestion, and dermal exposure [204]. The routes for uptake of the nanomaterials applied in different sections of the food industry will also be different. In this section, these three routes are discussed in detail.

Inhalation

During the production of nanomaterials in the food industry, it is inevitable that there will be some nanomaterials dispersed in the atmosphere. Hence, inhalation is the primary route for workers to uptake the NPs. The nanomaterials used in the food industry should be highly safe. However, many of them are not food-grade but applied in the food processing, especially the nutrient delivery. For instance, the NP used in the food security or food packaging such as QD or CNT is not food-grade. In addition, agricultural workers inhale nanopesticides when using them in agricultural cultivation.

Ingestion

Nanotechnology has good promise in the food industry especially in nutrient delivery. Then, ingestion will be the primary route for consumers. Since many of these nutrition nanocarriers are food-grade or GRAS, it is okay for human beings to uptake them. But one possibility should not be ignored. People may swallow inhaled nanomaterials when these deposited items are cleared by the mucociliary escalator [205]. In this case, ingestion becomes the secondary route for people exposed to nanomaterials. Few evidences demonstrate that these nanomaterials are eliminated rapidly [204]. Meanwhile, when nanomaterials in the packaging are released to the food or water, people will also ingest these NPs indirectly.

Dermal exposure

Skin is the first guard for the human body. Intact skin can protect the system from the invasion of foreigners, including the nanomaterials [162,206]. Therefore, dermal exposure should be the most important route for humans to contact nanomaterials. From the production of NPs in the food industry to the applications, humans can be exposed to nanomaterials at every section in the food industry. For example, in addition to the occupational exposure of workers, consumers contact nanomaterials released from the packaging and nanosensors, etc.

NANOTOXICOLOGY OF NANOMATERIALS USED IN THE FOOD INDUSTRY

Trends in nanotoxicological research of non-food nanomaterials

Nanotechnology has revolutionized almost every field of science. Although it brings benefits to consumers, it still has great possibilities to raise some risks or health concerns for the human body [207].

In the food industry, food safety is the primary issue. Hence, it is of great interest to assess the risk or health impacts of nanotechnology-based food materials. However, nanotoxicological research has generally focused on non-food nanomaterials so far. Since many nanomaterials can be applied in food packaging, food security, and water purification, these materials may contaminate the food and enter into the human body through the food chain. For instance, the Ag NP may release to food from the packaging. Currently, Yang et al. [208] reported that the nanosilver could bind with DNA and the replication fidelity of the rpsL gene was compromised by three types of Ag NPs, such as Ag nanopowder, Ag/Cu nanopowder and colloidal Ag, respectively. However, another study [209] showed that the nanosilver itself owned weak genotoxicity but illustrated obvious genotoxicity after combined with the detergent cetylpyridine bromide (CPB). Many lessons can be learned from the existing evidence for the nanotoxicity studies. Evidence showed that the inhaled NPs could lead to adverse effects in the lung and may also affect the cardiovascular system [210,211]. However, this does not mean that all of the nanomaterials were toxic to cells or tissues. Rieter et al. [212] found that amine/carboxylate/gadolinium functionalized amorphous Ag NPs were nontoxic to the PBMC from C57BL/6 mice. The physicochemical characteristics, including the size, surface chemistry, or modification, crystal type, and solubility, determine the activity and toxicity of nanomaterials [162]. Meanwhile, animals of different species have different sensitivity to nanomaterials. Bermudez et al. [213] investigated the subchronic inhalation toxicities of TiO_2 NP (21 nm) to mice, rats, and hamsters. The study shows that the hamsters could clear the NPs faster than the other two species. The distribution of the NPs in the system is another important factor. In addition to being deposited in the lung, the NPs (e.g., TiO_2) could also enter into the olfactory bulb through the olfactory nerve and migrate to the brain [214–216]. The distributions of the TiO_2 NP in the liver, spleen, and kidney were observed during the oral acute toxicity [217]. However, there are few studies on the GI tract [218]. The toxicological research in the digestion system is vital to the risk assessment of nanomaterials in the food industry. Paracelsus once stated that “all things are poison and not without poison; only the dose makes a thing not a poison”. In fact, the system can defend itself from the invasion of foreigners like nanomaterials. However, when translocated to the tissues or cells in a high concentration, it will result in particle overload in the tissues and then the functions of tissues will be impaired [219]. With more and more nanomaterials used in various fields, the concern of potential toxicity has been brought to the forefront. Table 2 summarizes the latest toxicological research on some nanomaterials that may be applied in the food industry. Although there is increasing information about the toxicities of nanomaterials, the general conclusions of the nanotoxicity of specific nanomaterials have not been formed until now. The differences of some characteristics and assay conditions may be the main reasons for the different results and even discrepancies among these research groups [233]. Therefore, there is an urgent need for establishing standard protocols to assess the risks of different kinds of nanomaterials [162,234]. In addition, due to the differences between humans and experimental animals, the conclusions cannot be drawn simply from the results of the animal experiments [235,236].

Table 2 Latest toxicological research of nanomaterials.

Nanomaterials	Properties	Models	Results	References
Nanosilver	6–20 nm	IMR-90, U251	Cause damage to mitochondria and DNA in dose-dependent manner especially in U251.	[220]
TiO_2 NP	10–20 nm, 20–30 nm, 30–50 nm, 50–80 nm, 80–300 nm	PB lung model, dermal and lung cells	The workers have no risk on lung inflammatory response but have significant risk on cytotoxicity response at high concentration at size range 10–30 nm.	[221]
	50, 285 nm	Nematode	Both NP and bulk counterpart were toxic, inhibiting growth and especially the reproductive capability of the nematode.	[222]
	10–20 nm, 10–120 nm	*P. scaber*	The effects of nano-TiO_2 were dependent on exposure concentration and duration, total consumed quantity, size, and pretreatment of particles. The exposure concentrations 10–1000 mg TiO_2/g dry food wereidentified as safe for *P. scaber*.	[223]
Carbon nanotube	100–150 nm × 10–20 μm	Mice	The implanted tubes with impurities clearly induced immunological toxicity and localized alopecia, whereas extremely pure implanted tubes showed good biocompatibility.	[224]
	1.1 nm × 0.5–100 μm	BEAS 2B cells	Showed genotoxicity at the lowest dose tested (10 μg/cm^2).	[225]
	17.5 nm × 0.7 μm	Zebrafish	Extensive purification and functionalization processes can help improve the biocompatibility of CNTs but the purified may have long-term toxicity effects when delivered into the body.	[226]
ZnO NP	30, 60, 200 nm	NSCs	ZnO NPs manifested dose-dependent, but no size-dependent toxic effects on NSCs (neural stem cells).	[227]
	20, 532 nm	Nematode	Both NP and bulk counterpart were toxic, inhibiting growth and especially the reproductive capability of the nematode.	[222]
	30 nm	Human epidermal cell line	ZnO NPs even at low concentrations possess a genotoxic potential in human epidermal cells.	[228]
	20–80 nm	Rat pyramidal neurons	10^{-4} g/ml ZnO NP disturbed the ionic homeostasis and the physiological functions of neurons.	[229]

(*continues on next page*)

Table 2 Latest toxicological research of nanomaterials.

Nanomaterials	Properties	Models	Results	References
Quantum dot	CdSe/ZnS-PLL(9 nm), CdSe/ZnS-PEG$_{350}$-OCH$_3$(7 nm), CdSe/ZnS-PEG$_{5000}$-NH$_2$(14 nm), CdSe/ZnS-PEG$_{5000}$-COO(14 nm), CdSe/ZnS-PEG$_{5000}$-OCH$_3$(14 nm)	Zebrafish embryo	At sublethal concentrations, many QD preparations produced characteristic signs of Cd toxicity that weakly correlated with metallothionein expression, indicating that QDs are only slightly degraded in vivo. QDs also produced distinctly different toxicity that could not be explained by Cd release.	[230]
	Thiol-CdTe, CdTe/CdS, CdTe/CdS/ZnS	K562, HEK293T	CdTe QDs are highly toxic for cells and the presence of a ZnS outlayer greatly improves the biocompatibility of QDs.	[231]
Au NP	9 nm	Single-donor fresh semen sample	After mixing the semen with Au NP solution, 25 % of sperm were not motile. Penetration of Au NP into the sperm heads and tails was observed.	[232]
Si NP	30, 48, 118, 535 nm	Mouse keratinocytes	Amorphous Si NPs below 100 nm induced cytotoxicity suggest size of the particles is critical to produce biological effects.	[174]

How to assess the risk of nanomaterials in the food industry scientifically

To completely understand the risks of nanomaterials in the food industry, there should be improvements or innovations of three aspects at least. First, the study methods need to be improved. Because of the novel properties of nanomaterials, there is a great challenge that the traditional methods may be not suitable for this newly emerging technology. Monteiro-Riviere et al. [237] reported that classical assays such as MTT, neutral red (NR), calcein AM (CAM), Live/Dead (LD) and Celltiter 96® AQueous One (96 AQ) are invalid for assessing the toxicities of nanomaterials (SWCNTs, QDs, carbon black, fullerenes) due to the interactions between carbon nanomaterials and the assay markers. They conclude that more than one assay is necessary to determine the toxicity of the nanomaterials. The complete and scientific characterization is the key issue to understanding the potential toxicity of the nanomaterials. Nowadays, nanometrology, the science of measurement at the nanoscale level [238], is playing an important role in characterizing nanomaterials. Jiang et al. [239] characterized systemically the important parameters that govern the stability of the NP dispersion, such as solution ionic strength, pH, surface charge, and surface coating. Meanwhile, new equipment will be developed to satisfy the rapid development of the nanotechnology. And the techniques and measurement should also be standardized [240]. With these methods, we can analyze nanomaterials including the NDS of the food industry systemically. However, food raises new challenges for the analytical techniques due to its complexity. Then, the NDS needs to be separated from the food. Bouwmeester et al. [241] reviewed the separation techniques for the NDS. Since elements play an important role in human life, it makes sense to analyze the detailed changes of a specific element after the nanomaterials are internalized into cells or tissues. Meanwhile, the quantified studies for the uptake of nanomaterials can be done through specific element analysis due to the nanomaterials usually composed of non-native elements within the human body. The metabolomics, metallomics, and elementomics can be very helpful, in particular, to fulfill the analysis of metallic NPs. Li et al. [242] reviewed these "omics" and analytical techniques at length. And currently, Marquis et al. [243] reviewed systematically the analytical methods for assessing nanotoxicity.

The second concern is that nanomaterials used in the food industry should be classified systemically. Meanwhile, the preparation methods of specific nanomaterials should be standardized. The dose of nanomaterials used in the food industry is also a very important parameter. As a result, consumers contact the nanomaterials at a low dosage. The workers may be exposed to nanomaterials at a high concentration during the manufacture. Hence, it is not scientific to draw the conclusion that a specific nanomaterial is harmful to the human body without being classified systemically. What is worse, it will make consumers refuse to enjoy food containing nanomaterials. This may hinder the development of food nanotechnology. After finishing systematic analysis, we can draw scientific and accurate conclusions and completely understand the mechanisms of nanomaterials.

The last but not least concern is the construction of suitable animal and other models. Sayes et al. [244] demonstrated that current in vitro cell culture systems do not accurately forecast the pulmonary hazard responses of instilled particles and the in vitro systems should be further developed, standardized, and validated. The useful data can be obtained from the proper animal model, which mimics the conditions exposed to humans best and provides useful guidelines for assessing the risks of nanomaterials to humans.

To assess the toxicity of the nanomaterials is not just to know whether they pose a health risk or not and how severe the toxicity is. The greatest role of the nanotoxicity is to provide guidelines for us to minimize the toxicity and optimize their application. In other words, we should know how to manage the risks of nanomaterials and make full use of them while understanding the nanotoxicities and the mechanisms of the nanomaterials. Figure 2 shows clearly how to maximize applications of nanotechnology and enjoy life while managing their risks scientifically. It is embarrassing that nanomaterials are being used in almost every field while we do not completely understand the health concerns. Therefore, it is imperative that we unveil the risks of nanomaterials. As shown in Fig. 2, we will embrace our dream of the future as long as we can control the relationships among scientific assessments, applications, and risk management.

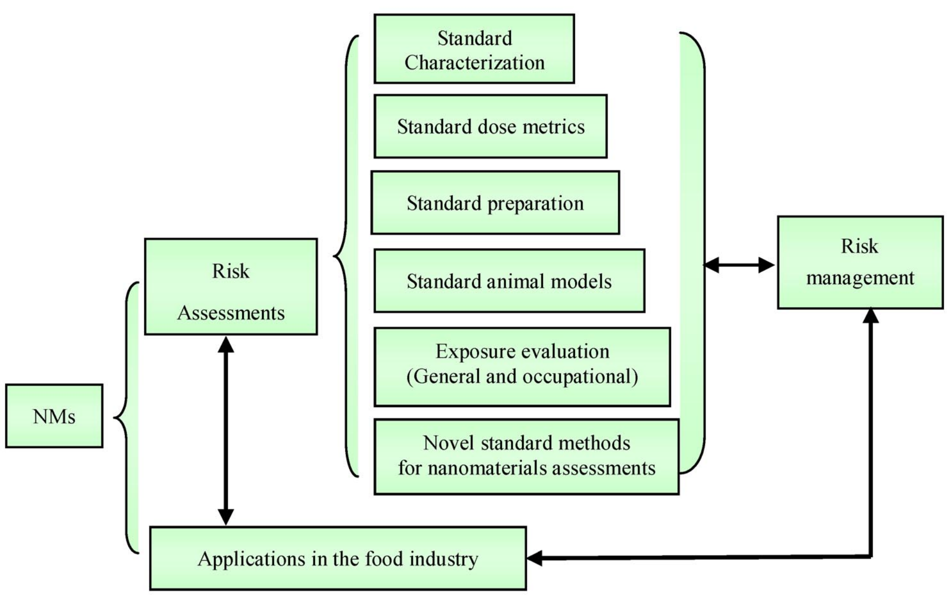

Fig. 2 Possible risk assessment and management of nanomaterials and nanotechnology in the food industry.

SUMMARY AND OUTLOOK

Nanomaterials with their novel physicochemical properties have been applied in the food industry and related fields such as agricultural cultivation, food processing, food packaging, food security, and water purification. Nanotechnology can bring great benefits to human beings. However, they may have negative effects on the environment, ecosystem, and humans. There are many determinants for the activities and toxicities of nanomaterials involving particle size, chemical composition, surface structure, dosage, etc. Nanomaterials can enter the human body through three main routes, inhalation, ingestion, and dermal exposure. In addition to nutrient delivery, consumers will be exposed to nanomaterials if they are released into food or the food chain. There is also potential occupational exposure to the workers. Hence, there is an increasing interest to assess the risk of nanomaterials. In a word, nanotechnology will benefit human beings greatly under the proper regulation and scientific assessment. The establishment of a regulatory system for manufacturers using nanomaterials or nanotechnology in food products and proper labeling for the public is timely and obligatory.

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