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Ensuring Global Food Safety

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https://doi.org/10.1016/B978-0-12-816011-4.00016-1

Chapter 16

Nanotechnology and food safety

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16.1 Introduction

Nanoscale objects are not new; they have been known to exist for decades. Yet, it was the ability of scientists to see and engineer nanostructures via self- or directed assembly in the 1980s that catalyzed their rapid development. Nanotechnology has now evolved into a convergent discipline involving a variety of sciences (physical, chemical, biological, engineering, and electronic) designed to understand and manipulate structures and devices at nanoscale. The use of nano-based consumer products is growing rapidly and many such products are available in the market. To date, more than 1800 consumer products that are self-identified by the manufacturers as containing nanotechnology are included in the public database (Project on Emerging Nanotechnologies, 2018). Nano-based goods are projected by various sources to be an estimated $2.6 trillion global industry by 2014 (ScienceDaily, 2007) and a nano-dominated future is not too distant.

A nanomaterial is generally defined as "a discrete entity that has one or more dimensions of the order of 100 nm or less" (SCENIHR, 2007b). Unique properties of these materials arise at the nanoscale where they do not behave like their macroscale counterparts. The physico-chemical properties of nanostructures are not governed by the same laws as larger structures, but by quantum mechanics. Color, solubility, diffusivity, material strength, toxicity, and other properties will be very different at the nanoscale as compared to the macroscale. Other important properties include increased reactivity because of quantum mechanical effects in combination with the high (relative) surface area of nanostructures, which allows the creation of genuinely new properties and materials with desired functionalities. The potential benefits for application of nanotechnologies in food have been widely discussed and cover many aspects such as efficient nutrient delivery, formulations with improved bioavailability, novel antimicrobials, new tools for molecular, and cellular detection of contaminants and food packaging materials (Chaudhry et al., 2008; Moraru et al., 2003, 2009; Feng et al., 2014, 2015; Chen et al., 2006; Das et al., 2008; Weiss et al., 2006; Luksiene, 2017).

As new applications emerge, there is also growing concern, both from the public and the scientific community, about the potential risks and toxicity of nanotechnology products, or the environmental and personal safety aspects of their use. The fact that size matters as it influences efficacy and safety, the question arises whether a nanoscale particle that has unique material properties should be deemed new or nonnatural for purposes of safety evaluation. A lack of knowledge of how nanoscale structures may interact with biological systems and potentially create safety issues is often cited as the last hurdle to overcome in their acceptability in food and pharmaceutical applications.

The purpose of this chapter is to explore the global safety and regulatory issues associated with the application of nanotechnology to food systems. Emphasis is placed on the toxicological knowledge needed to perform a hazard assessment and the lack of measurement technologies for exposure assessment. Additionally, the current state of the regulatory food safety framework is described, and the consequences of the scientific knowledge gaps that exist in the application and enforcement of the current regulations are highlighted.

16.2 Nanotechnology and food systems

Food science and technology has made many micro- and often nano-size food particles by utilizing either the top-down (e.g., grinding, microparticulation, micronizing) or bottom-up (e.g., molecular aggregation) approaches. The advent of nanotechnology has ushered in new scientific and technological opportunities for the food industry, but the uncertainty

Ensuring Global Food Safety. https://doi.org/10.1016/B978-0-12-816011-4.00016-1

remains whether small sized material should be treated as new entities when compared to their larger forms (Chau et al., 2007). Efforts are underway worldwide to most responsibly realize the benefits of nanomaterials without exposing the public and environment to harm. Controlled cross-linking, inhibition of droplets coalescence, and generation of multilayered structures are just a few generic examples of the role of nanotechnology. To date, the key areas of food nanotechnology research, development, and application include the following:

16.2.1 Structure and function characterization and modification

Macro components of food, protein, carbohydrates, and fat constitute a set of nanostructures that are ideally suited for targeted advances via nanotechnology. A vast majority of food carbohydrates and lipids are one-dimensional nanostructures of less than 1 nm in thickness, while globular proteins are nanoparticles of 10−100 nm in size. An understanding of the behavior and functionality of these nanostructures can be profitably used to set up processing strategies to improve food structure. Availability of new physical tools like the atomic force microscope (AFM) to study nanostructures has proven invaluable in understanding food structure−function relationships. AFM has been successfully used to quantify properties like stiffness, hardness, friction, elasticity, or adhesion at the molecular level. The ability to manipulate individual biomolecules using AFM has allowed the study of structural and phase transitions, nanorheological, and nanotribological properties of polymers (Strick et al., 2000; Terada et al., 2000; Morris et al., 2001; Nakajima et al., 2001; Boskovic et al., 2002). The gelation ability, the mechanisms of gelation, and the microstructure of the resulting gels were studied for biopolymers such as gums and proteins (Gajraj and Ofoli 2000; Ikeda et al., 2001; Morris et al., 2001). Recent development in AFM imaging modes such as multiparametric, molecular recognition, multifrequency, correlative, and high-speed imaging further expands the capabilities of this powerful tool in understanding structure−function relationships in complex biological and food systems (Dufrêne et al., 2017).

The development of new generation scanning probe microscopy (SPM) instrumentation, including the near-field scanning optical microscope, scanning thermal microscope, scanning capacitance microscope, magnetic force and resonance microscopes, and scanning electrochemical microscope, further enhanced the capability of investigations at the nanoscale. By combining SPM and AFM with other imaging, mechanical, and spectroscopic methods, it is now possible to quantitatively characterize the structures of polymers at the micrometer and nanometer level, as well as the intra- and intermolecular forces that stabilize such structures. Nonintrusive determination of local phase behavior and structure in complex biopolymer matrices could ultimately lead to improved control and design of the quality and stability of foods.

Fabrication at the nanoscale opened windows of opportunity for the creation of new, high-performance materials with applications in food processing, packaging, and storage. For example, nanotechnology approaches have been used to develop nanoparticles enhanced polymeric membranes for applications such as purification of ethanol and methanol (Jelinski, 1999; Kingsley, 2002) and packaging materials with low gas permeability (Duncan, 2011). Another novel solution for enhancing membrane functionality is based on the use of nanotubes.

Nanotubes are long and thin tubes that can be assembled in extremely stable, strong, and flexible honeycomb structures. Nanotubes are the strongest fibers known—one nanotube is estimated to be 10−100 times stronger than steel per unit weight. By functionalizing nanotubes in a desired manner, membranes could be tailored to efficiently separate molecules both on the basis of their molecular size and shape and on their chemical affinity. High selectivity nanotube membranes can be used both for analytical purposes, as part of sensors for molecular recognition of enzymes, antibodies, proteins and DNA, or for the membrane separation of biomolecules (Huang et al., 2002; Lee and Martin 2002; Rouhi, 2002; Siwy et al., 2005).

Another application of nanotubes is the fabrication of nanotube-reinforced composites with high fracture and thermal resistance. Such materials could replace conventional materials in the manufacture of a wide range of machinery, including food-processing equipment (Gorman, 2003; Zhan et al., 2003; Raviathul Basariya et al., 2014; Chen et al., 2017). While such technologies are still too expensive for commercial scale food applications, it can be foreseen that they would become feasible for food-related applications in the not so distant future.

16.2.2 Nutrient delivery systems

Nanostructures in foods can be designed for the targeted delivery of nutrients in the body for the most beneficial effects. By facilitating a precise control of properties and functionality at the molecular level, nanotechnology enabled the development of highly effective encapsulation and delivery systems. Examples include nanometer-sized association colloids such as surfactant micelles, vesicles, bilayers, reverse micelles, or liquid crystals. Such systems could be used in food applications as carrier or delivery systems for vitamins, antimicrobials, antioxidants, flavorings, colorants, or preservatives (Weiss et al., 2006; Jafari and McClements, 2017).

Nanospheres have been proven to have superior encapsulation and release efficiency as compared to traditional encapsulation systems (Riley et al., 1999; Weiss et al., 2006; Jafari and McClements, 2017). Nanoscale encapsulation systems can be produced using food biopolymers such as proteins or polysaccharides, which then can be used to encapsulate functional ingredients and release them in response to specific environmental triggers. Dendrimer-coated particles and cochleates can also be used as efficient encapsulation and delivery systems (Santangelo et al., 2000; Khopade and Caruso, 2002; Gould-Fogerite et al., 2003). Cochleates can be used for the encapsulation and delivery of many bioactive materials, including compounds with poor water solubility, protein and peptide drugs, and large hydrophilic molecules (Gould-Fogerite et al., 2003). Another solution for encapsulation of functional components is via nanoemulsions. The advantage of nanoemulsions is that they can enable the slowdown of chemical degradation by engineering the properties of the interfacial layer surrounding them (McClements and Decker, 2000). Such systems could potentially be used for the encapsulation and targeted delivery and controlled release of functional food molecules.

16.2.3 Sensing and safety

Nanotechnology has benefited the area of food safety mostly through the development of highly sensitive biosensors for pathogen detection and the development of novel antimicrobial solutions. Fellman (2001) reported the development of a method to produce nanoparticles with a triangular prismatic shape for detecting biological threats such as anthrax, smallpox and tuberculosis, and a wide range of genetic and pathogenic diseases. Latour et al. (2003) investigated the ability of two types of nanoparticles to irreversibly bind to certain bacteria, inhibiting them from binding to and infecting their host. One type was based on inorganic nanoparticles functionalized with polysaccharides and polypeptides that promote the adhesion of the targeted bacterial cells. This research has the potential to reduce the infective capability of human food-borne enteropathogens such as *Campylobacter*, *Salmonella*, and *Escherichia coli* in poultry products (Latour et al., 2003). Kuo et al. (2008) successfully developed a bioconjugation procedure that allows the attachment of water-soluble cadmium tellurium semiconductor quantum dots to anti-*E.coli* antibody. Such quantum dots are promising probe materials in the development of antibody-based immunosensors with high stability, sensitivity, and reproducibility, that could allow the detection of a single pathogenic cell (Kuo et al., 2008). Jin et al. (2009) showed that quantum dots made out of zinc oxide could be effective at inhibiting pathogens such as *Listeria monocytogenes, Salmonella enteritidis*, and *Escherichia coli* O157:H7, which further demonstrated the promise of nanoparticles for food safety applications.

16.2.4 Antimicrobials

Advances in nanoparticle synthesis have given rise to a variety of nano-enabled or nano-enhanced antimicrobials that hold great promise in improving food safety. Compared to their bulk counterparts, nanoparticles-based antimicrobials have increased activity owing both to their small size, which facilitates penetration of cellular membranes, and to a high surface-area-to-volume ratio, which increases the number of active sites and/or boosts the release rate of active components (Lemire et al., 2013; Bastarrachea et al., 2015).

Metal-based nanoparticles have garnered increasing attention due to their excellent antimicrobial effects. For instance, silver and copper in their bulk solid form have been long known for their capability of disinfecting water and preserving food (Castellano et al., 2007). Recent development of metal oxide nanoparticles, including silver, gold, copper, aluminum, zinc oxide, and titanium oxide, started to reveal their exceptional potential as alternatives to conventional chemical antimicrobials in food systems (Luksiene, 2017). The currently accepted antimicrobial mechanisms of metallic nanoparticles include generation of reactive oxygen species, release of metal ions, and nonoxidative mechanisms (Wang et al., 2017). One important advantage of metallic nanoparticles over conventional chemical-based antimicrobials is that metallic nanoparticles can effectively lower the risk of developing antimicrobial resistance by attacking a broad range of targets of the microbial cells, including DNA and some intracellular proteins, which limits the chance of developing mutations necessary for the microorganisms to survive (Lemire et al., 2013; Luksiene, 2017). As the threat of multidrug-resistant bacteria is increasing globally (Norrby et al., 2005; Roca et al., 2015), metallic nanoparticles may become a very attractive alternative to some of the existing antimicrobials that are known to induce microbial resistance.

Nanoparticles can also enhance the antibacterial activity of chemical antimicrobials, due to the dramatic increase in the number of active sites, enabled by the high specific surface area of nanoparticles. Nanoparticle-associated antimicrobials have been found to exhibit superior stability over their free-form counter-parts, which is important for their long-term biocidal activity (Jain et al., 2014). One such example is the combination of nanoparticles with quaternary ammonium (QA) compounds, which are among the most promising antimicrobial chemicals for food and agriculture systems, thanks to their high biocidal activity, long-term effectiveness, and environmental friendly nature. Song et al. (2011) showed that

silica nanoparticles functionalized with QA exhibited enhanced antimicrobial efficacy against growth of *E. coli* and *S. aureus* compared to silica nanoparticles alone, and the biocidal performance of QA-modified silica nanoparticles improved with decreasing size of the nanoparticles. Nanoscale structures such as dendrimers can further enhance the surface density of antimicrobial compounds. Wen et al. (2012) synthesized a core shell type dendrimer nanoparticles featuring a high-density QA shell that improved water solubility and antimicrobial ability. Future research on the synergistic effects between antimicrobial compounds and various nanostructures may provide novel, highly effective bactericidal solutions.

In spite of their great promise, one caveat in using nanoscale metallic antimicrobials in the food industry is that their effectiveness can be impaired by the interactions with organic compounds that exist in abundance in food systems (Noyce et al., 2006). The other limitation lies in public health and environmental concerns about migration of metallic nanoparticles (Lemire et al., 2013; Llorens et al., 2012; Marambio-Jones and Hoek 2010; Rai et al., 2009). For instance, although some silver-based coatings are listed by the US Food and Drug Administration (FDA) in their Inventory of Effective Food Contact Substance Notifications (FDA, 2018), the use of silver and silver zeolite−based antimicrobial materials in food applications is currently limited.

16.2.5 Food packaging and tracking

The use of nanostructured materials, particularly nanocomposites, could considerably enhance the functional properties of packaging materials, and thus improve the shelf life of packaged foods. Nanocomposites are made out of nanoscale structures with unique morphology, increased modulus, and strength, as well as good barrier properties. For example, a packaging material made out of potato starch and calcium carbonate that has good thermal insulation properties, lightweight, and biodegradability was proposed as a replacement for the polystyrene "clam-shell" used for fast food (Stucky, 1997). Nanocomposites are also regarded as a potential solution for plastic beer bottles (Moore, 1999). Natural smectite clays, particularly montmorillonite, a volcanic material that consists of nanometer-thick platelets, can be used as an additive that makes plastics lighter, stronger, more heat resistant, with improved oxygen, carbon dioxide, moisture, and volatile barrier properties (Quarmley and Rossi, 2001). Nanocomposites based on starch and reinforced with tunicin whiskers (Mathew and Dufresne, 2002) or clay nanocomposites (Park et al., 2003) have also been developed in recent years. A nanocomposite material based on chitosan and reinforced with exfoliated hydroxyapatite layers was developed by Weiss et al. (2006).

Coatings or films for food packaging materials could also be made using nanolaminates and nanofibers. Nanolaminates consist of two or more layers of material with nanometer dimensions physically or chemically bonded to each other. Nanolaminates can be made using the layer-by-layer deposition technique, which allows precise control of the thickness and properties of the nanolaminates (Weiss et al., 2006). Nanofibers are polymeric strands of submicrometer diameters produced by interfacial polymerization and electrospinning. Electrospun polymer fibers have unique mechanical, electrical, and thermal properties, and have applications in filtration, manufacturing of protective clothing, and biomedical applications. Production of nanofibers from food biopolymers in the future might increase their use in the food industry for a range of applications, including packaging materials (Weiss et al., 2006). In addition to pursuing improved functional properties of packaging materials, nanocomposite research has also expanded into developing smart packaging (e.g., enzyme immobilization, indicators of temperature abuse of product during its manufacturing and shelf life), green synthesis of nanomaterials, antimicrobial packaging, or materials with improved recyclability and biodegradability (Rhim et al., 2006, 2013; Yoksan and Chirachanchai, 2010).

Food traceability is another important area where nanotechnology is playing an increasingly important role. Within the context of agri-food system, according to Costa et al. (2013), traceability can be defined as "the ability to locate an animal, commodity, food product, or ingredient and follow its history in the supply chain forward (from source to consumer) or backward (from consumer to source)." For example, some efforts in nanotechnology-based detection and tracking targeted the meat industry, with nanobarcodes that were incorporated into animals through feed or direction injection to create unique identification that would last through the lifecycle of the animals and the resulting products (Kuzma, 2010). Such nanobarcodes could allow tracking of feed contamination, tracing animal products from farm to fork for supply chain management, and ensuring food safety. Despite the promising applications, nanobarcodes incorporated into food have raised concerns in some consumer groups, as such a tracking system may infringe upon consumer and company privacy; additionally, the environmental and health ramifications of the nanoparticles used in this technology need to be carefully studied before implementation on a large scale (Kuzma, 2010).

Product tracking can also be accomplished via packaging, which circumvents most of the abovementioned concerns associated with nanosized tags inside food products. Among the available tracking technologies compatible with food

packaging applications, Radio Frequency Identification (RFID) technology has shown the most promise (Costa et al., 2013), thanks to its long detection range, fast reaction speed, minimal user effort, unique identification of every individual item/product, and simultaneous reading of information from more than one tag. Despite all the advantages of RFID technology over traditional barcodes, its market penetration is largely hampered by its high cost, which a few years ago started at 7 US cents per RFID tag, much higher than the "less than 1 US cent" target for it to become economically feasible for food packaging (BRIDGE, 2007). Yet, as it is the case with any new technology, costs are coming down as the technology develops. For instance, Jung et al. (2010) successfully printed the electronics of an RFID tag with single-walled carbon nanotube (SWCNT)—based ink and demonstrated a practical way to scale up the production with a roll-to-roll process on plastic foils. The exceptional electric properties of SWCNT and their high dispensability in solvent enabled the scalable and deterministic printing of RFID tags (Jung et al., 2010; Cao et al., 2008; Ahn et al., 2006). This represents a clear example of how nanotechnological breakthroughs in fields not directly related to food can help solve one of the most challenging problems in the agri-food system including food traceability and food safety.

16.3 Current status of regulation of nanomaterials in food

The need for information and scientific advice on the safety implications that may arise from the use of nanotechnology in food and agriculture was recognized by the World Health Organization (WHO) and the Food and Agriculture Organization (FAO) of the United Nations. These organizations decided to work together on identifying knowledge gaps in areas related to food safety, risk assessment procedures, as well as on developing global guidance on adequate and accurate methodologies to assess potential food safety risks that may arise from nanoparticles. This collaborative effort will focus on both the application of nanotechnology in the primary production of foods, in food processing, packaging, and distribution, as well as the use of nano-diagnostic tools for detection and monitoring in the food and agriculture production. According to information posted on the FAO website (http://www.fao.org), the issues that will be addressed jointly by the two agencies include: (a) on-going research and development on nanotechnologies for use in the food and agriculture sectors that are expected to reach market within the next 10 years; (b) investigations of nanoparticle migration from food contact materials into foods; (c) purity, particle size distribution, and properties of nanoparticulate substances for use in foods and food contact surfaces; (d) mechanistic understanding of the behavior of nanoparticles in the body; (e) nanoforms of vitamins and nutrients in relation to their bioavailability, interference with the absorption of other nutrients, and consideration of safelimits; (f) interactions of nanoparticles with biomolecules, nutrients and contaminants, and their relevance to human health; (g) techniques for detecting, characterizing, and measuring nanoparticles in foods and food contact materials; (h) risk assessments of nanomaterials for use in foods and food contact surfaces; (i) information on nanodiagnostic tools in the food and agriculture sectors; (j) public perceptions of the applications of nanotechnologies to the food and agriculture sectors; and (k) identification of needs and priority areas for scientific advice needed in safety management and regulation by national authorities.

The last issue listed above is of particular importance, as regulation of nanotechnology is still in its infancy, and there is a great deal of variability in how this topic is addressed from country to country. A brief overview of the current status of regulating nanotechnology products that are relevant for the food and agriculture sectors is provided below.

16.3.1 North America

In the United States, the government agency responsible for regulating food, dietary supplements, and drugs is the FDA. However, it must be noted that dietary supplements fall under a different set of regulations than those covering "conventional" foods and drug products. The fact that some of these products, especially dietary supplements, are currently manufactured using nanotechnology creates an additional layer of complexity, as size has not been addressed so far by existing regulations. Under current US legislation, an ingredient or substance that will be added to foods is subject to premarket approval by FDA, unless its use is generally recognized as safe (GRAS). Yet, at this point, there is no information or guidance on how existing listings for food additives and GRAS substances apply to nanoscale materials. Clarification in this area has been identified by many policy experts as an urgent need, because otherwise products that contain nanoscale ingredients could be placed on the market without FDA clearance.

In a statement posted on its official website (http://www.fda.gov), the FDA states that it regulates products, not technologies, and that "nanotechnology products will be regulated as 'Combination Products' for which the regulatory pathway has been established by statute." At the same time, recognizing the challenges associated with the development of nanoproducts, the FDA issued in July 2007 a "Nanotechnology Task Force Report." The report is public and available at http://www.fda.gov. This report acknowledges that nanoscale materials could be potentially used in most product types

regulated by the FDA and that such materials present challenges because properties relevant to product safety and effectiveness may change at the nanoscale. This report recommends that FDA provides guidance regarding when the use of nanoscale materials changes the regulatory status of foods, food additives, food contact substances, or dietary supplements.

Efficient and strict regulations about nanotechnology cannot be passed, however, without a proper understanding of the potential risks associated with nanoproducts. The House Science and Technology Committee is currently looking into the need to strengthen federal efforts to learn more about the potential environmental, health, and safety risks posed by engineered nanomaterials. This was done following Environmental Protection Agency (EPA) recommendations for improving federal risk research and oversight of engineered nanomaterials by the EPA, FDA, and the Consumer Product Safety Commission. The report, "Nanotechnology Oversight: An Agenda for the Next Administration," published by the Project on Emerging Nanotechnologies (PEN) (Davies, 2008), offers a range of proposals on how Congress, federal agencies, and the White House can improve oversight of engineered nanomaterials.

The report "Review of the Federal Strategy for Nanotechnology-Related Environmental, Health and Safety Research" (National Research Council, 2008) identified serious weaknesses in the National Nanotechnology Initiative (NNI) plan for research on the potential health and environmental risks posed by nanomaterials. Among other observations, the report states that the NNI plan fails to identify important areas that should be investigated, such as a more comprehensive evaluation of how nanomaterials are absorbed and metabolized by the body and how toxic they are at realistic exposure levels. Significant criticism stemmed from the fact that the NNI plan does not address the current lack of studies on how to manage consumer and environmental risks, or mitigate exposure through consumer products. The report called for a revamped and comprehensive national strategic plan to minimize the potential risks of nanotechnology, which will allow the society to fully benefit from the discoveries of this technology in areas like medicine, energy, transportation, and communications.

In a significant development, Canada is planning to become the first country in the world to require companies to detail their use of engineered nanomaterials. This information is meant to help evaluate the risks of engineered nanomaterials and will be used toward the development of a regulatory framework (Heintz, 2009). This action came shortly after the Office of Pollution Prevention and Toxics of the US EPA released in January 2009 an interim report on the Nanoscale Materials Stewardship Program (NMSP) (EPA, 2009). NMSP was developed to help provide a firmer scientific foundation for regulatory decisions by encouraging submission and development of information about nanoscale materials. Under the NMSP Basic Program, EPA invited participants to voluntarily report information on the engineered nanoscale materials they manufacture, import, process, or use. Under the NMSP In-Depth Program, EPA invited participants to work with the Agency and others on a plan for the development of data on representative nanoscale materials over a longer time frame.

16.3.2 Europe

It is clear from a number of regulatory reports that there is currently no nano-specific regulation in the European Union (EU) (Chaudhry et al., 2008), or other countries (Hodge et al., 2007). However, the EU's approach to nanotechnology is that "nanotechnology must be developed in a safe and responsible manner" (EC recommendation, 2008). To that end, the EU has commissioned the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) to make an inventory to check whether nanotechnologies are already covered by other community legislation, thus defining the legislative framework, considering both implementation and enforcement tools for this specific framework. It was concluded that the EU regulatory framework in principle also covered nanotechnologies (SCENIHR, 2007a). In line with this, EU member states will aim to modify existing laws and rules as and when developments within the fields of nanoscience and nanotechnology render such measures necessary (Franco et al., 2007; Health Council Netherlands, 2006). Recently, the European Food Safety Authority EFSA was asked for a scientific opinion on the need for specific risk assessment approaches for technologies, processes, and applications of nanoscience and nanotechnologies in the food and feed area. While EFSA recognized the limited knowledge on possible food applications and the limited knowledge on the nanotoxicology, it considered the currently used risk assessment paradigm applicable for nanoparticles in food (EFSA, 2021).

16.3.2.1 Nano-size and regulations

The European General Food Law (GFL) is the umbrella of EU's food safety regulations (EC/178/2002, 2002). According to the GFL, all foods placed on the Community market must be safe ("Food shall not be placed on the market if it is unsafe"; where unsafe is defined as "injurious to health" or "unfit for human consumption" article 14 sub 1). In making an assessment of food safety, producers, among others, are required to take into account the probable immediate, short-term and/or long-term effects on the consumer and subsequent generations. The GFL stipulates that it is the responsibility of "food business operators" to ensure that their foods satisfy the requirements of food law. This regulation clearly stipulates

that in decision-making, scientific risk assessment should be central. The GFL stipulates that if after assessing the available information a possibility of harmful effects on health is identified but scientific uncertainty persists, risk management measures to ensure a high level of health protection may be adopted. Pending gathering and developing further scientific information for a more comprehensive risk assessment, the GFL allows the application of the precautionary principle.

Chemicals or substances intentionally added to food need to be authorized, meaning that in general a safety assessment of the material has been made before its market entry. In order to conduct a safety assessment, sufficient toxicological hazard information should be made available by the producers of the substance. This will also be the case for nano-substances subjected to authorization. However, in the existing European food safety legislation, no reference is made to nanotechnology or the nanosize of chemicals.

Authorization procedures, legislation, guidelines, and guidance documents describe how and which toxicity tests should be performed. Adjustments of legislation in particular, guidelines and guidance documents concerning the testing of nanoparticles are considered to be necessary (SCENIHR, 2007a). In particular, information concerning the physico-chemical parameters—e.g., particle size, particle form, surface properties, and other properties that may impact the toxicity of the substance—should be included. In addition, the validity of currently used toxicological assays—such as an OECD (Organisation for Economic Co-operation and Development) safety test protocols—for the detection of "novel" nanoparticle related effects needs to be determined. The currently used assays are validated for the toxicity testing of bulk chemicals. Furthermore, appropriate dose metrics to use in the hazard characterization and consumer exposure assessments of nanostructured materials should be developed. Thresholds or limits already set may not be appropriate for nanosized variants of the particular substances.

If a substance in its conventional form has been evaluated, reevaluation of the nano-sized form may be necessary. One should be aware that each new nano-sized form of a certain chemical probably has to be considered as a separate new compound, as long as size–effect relationships are not established for that compound. This underscores the need for taking into account the effect of particle size (including distribution of the size) in toxicological studies.

16.3.2.2 Monitoring the products containing nanotechnology on the market

A requirement in the GFL is that member states should monitor to verify if the requirements of food law are fulfilled by food business operators. Also the EFSA should establish monitoring procedures to identify emerging risks. The monitoring of nanoparticles will require the development of new analytical detection and confirmation techniques.

The Novel Food Regulation (EC/258/97) can be very relevant for nanotechnology in food. This regulation addresses "production processes not currently used," making it likely that this regulation also covers nanotechnology because of its novelty. It is not clear, however, whether the use of nano variants of chemicals in foods already on the market makes these foods "novel" and thus requiring authorization. The Novel Food Regulation is under revision at this moment, which creates an opportunity to sort out nanotechnology related issues.

In conclusion, the current food safety legislative system should be adapted but not rewritten to cover nanotechnologies, while it continues to protect the European consumer. The discussions on definitions of nanotechnologies and nanoparticles continue within, for example, the scientific committees of the European Commission but also globally within ISO (IRGC, 2008). The outcome will have a direct effect on the regulatory framework within Europe. However, there are serious concerns on the sensitivity of current toxicity assays; these concerns are addressed in the next section.

16.4 Hurdles in evaluation and regulation of the use of nanotechnology in foods

Food safety regulations require scientific safety assessments of foods and their ingredients, and this applies to nano-sized substances as well. While EFSA considered the currently used risk assessment paradigm also applicable to nanoparticles in food (EFSA, 2009), it is also clear that this is severely hampered by the limited scientific knowledge of the biological interactions of nanoparticles and on consumer exposure (Bouwmeester et al., 2009; EFSA 2009). The following section will focus on the main scientific knowledge gaps that currently hinder the safety assessment of nanoparticles in food and related products.

16.4.1 Lack of a good definition

The lack of a good definition of nanotechnology is problematic from a governance point of view. There are currently many definitions of nanotechnology available. Unfortunately, these either are too rigid to be applicable for food applications, or they are too flexible to be useful in legislation since they do not specify clear boundaries. The rigid definitions, e.g., the ones that specifically mention that nanotechnology refers to dimensions of less than 100 nm, open the possibility that

applications that use structures of slightly more than 100 nm need not conform to the regulation. If the definition is too flexible—e.g., if it refers to sizes of "about 100 nm," although it is scientifically more accurate—it cannot be used in legal texts. Something as simple as labeling cannot be enforced at the moment because of the lack of a clear definition of nanomaterials, which allows industry to maintain a lack of transparency. For instance, the food industry is actively exploring the applicability of nanotechnology in food products, but is reluctant to admit to that.

16.4.2 Detection of manmade nanomaterials in complex matrices, including foods

Governance of applications of nanotechnology requires regulation of its use. Regulation in turn requires legislation and enforcement. Without means to enforce the regulation, the governance is useless and only constitutes an administrative process that does not really provide the protection against unwanted effects that the governance is seeking. Unfortunately, one key issue that hinders the enforcement of regulations related to the use of nanotechnology products is the capacity to detect nanostructures. Enforcement implies that manmade nanomaterials can be detected even if manufacturers of the products deny the use of nanotechnology.

Whereas the characterization of bulk chemical compounds in foods is usually relatively straightforward, characterization of nanoparticles is much more complex, due to several reasons. First, from an analytical point of view, there is not a single (or a handy) analytical toolkit that allows the full characterization of nanoparticles in food. At present, there is a vast array of analytical techniques available to characterize nanoparticles, both single-particle techniques and techniques for characterizing the assembly of engineered nano materials (ENMs) is simple solvents (Powers et al., 2006; Hassellov et al., 2008; Luykx et al., 2008; Tiede et al., 2008; Minelli et al., 2019). Food and other biological samples and agricultural samples are heterogeneous mixtures. Characterizing the ENMs from these matrices requires separation or pretreatment to isolate the ENM from the interfering matrix components (Bouwmeester et al., 2014). Due to their high reactivity, nanoparticles can change in composition and size as a response to changes in their environment. Ideally, sample preparation is kept minimal (Szakal et al., 2014). An example of a powerful approach that has been developed in recent years is single particle ICP-MS (sp-ICPMS) in which nanoparticles can be detected with limited sample preparation. In sp-ICPMS individual nanoparticles are atomized and ionized using ICP plasma and the resulting plume of ions is detected by the MS. Detection limits are generally in the ng/L range. A great advantage of sp-ICPMS is that it determines a number-based size distribution (Peters et al., 2014, 2018). Generally, these methods are only able to determine one single characteristic; and currently, it is practically impossible to fully characterize nanoparticles. Therefore, research should primarily focus on method development for the detection and characterization of nanoparticles. Ideally, such methods should be relatively easily performed, and use equipment that is currently present at laboratories equipped for detection of chemicals in food. Interestingly, some of the definitions of nanoparticles introduce the specific functionalities of nanoparticles compared to the larger scale equivalents. While it might be difficult to define specific functionalities in general terms, this opens an alternative avenue for the characterization of nanoparticles: effect characterization. For this approach, in vitro assays searching for biomarkers for exposure might be a very elegant alternative.

Secondly, at the moment it is virtually impossible—apart from some very specific cases—to distinguish between manmade and natural nanoscale structures. Multielement analysis of single nanoscale structures might be a direction to further investigate (Naasz et al., 2018). Lastly, from a toxicological point of view, there is a lack of knowledge on how to describe biological dose–response relations, i.e., which metrics need to be used to express these relations. Up to now, it has not been possible to establish a single dose–describing parameter that best describes the possible toxicity. It is likely that mass alone is not the good metric (SCENIHR, 2007a), but other characteristics such as size specific surface area, surface charge (Zeta potential), as well as the number of particles per particle size might be very useful for describing the dose (Hagens et al., 2007; McNeil, 2009; Oberdorster et al., 2007a). Given the complexity of the matter, it is reasonable to say that the scientific requirements for analytical tools for nanostructures cannot be fully formulated yet.

16.4.3 Assessment of exposure to nanoparticles

Exposure assessment is defined as the qualitative and/or quantitative evaluation of the likely intake of biological, chemical, or physical agents via food, as well as exposure from other sources if relevant (FAO/WHO, 1997). The reliability of the exposure assessment is critically depending on the availability of analytical tools to determine the presence or absence of nanoparticles in food. Basically, the principle of assessing exposure to nanoparticles via food will be comparable to the exposure assessment of conventional chemicals. Usually one of the following three approaches is applied for integration of data: (1) point estimated; (2) simple distributions; and (3) probabilistic analyses (Kroes et al., 2002). Issues like food sampling and variability within composite samples, variation in concentrations between samples, and consumption data on

specific food products are not different from those encountered when assessing the exposure to conventional chemicals. Alternatively, food processors should provide reliable data on the use of nanoparticles in their products. The quality and reliability of the exposure assessment will be greatly improved if the concentration data are collected in an occurrence database. The last step in performing exposure assessment is the integration of occurrence and food consumption data. The procedures used here are not different from the ones used for conventional chemicals.

16.4.4 Toxicity of nanoparticles

Knowledge on the potential toxicity of nanoparticles is rapidly growing. Original work suggested that nanoparticles may have a deviating toxicity profile when compared to their bulk equivalents (Oberdorster et al., 2005a, 2007b; Donaldson et al., 2001; Nel et al., 2006).

After nanomaterials enter the body via the oral route, they are subjected to conditions that are very different from those encountered via other exposure routes. The extremely low pH of the stomach and the high ionic strength in the stomach and intestine will critically affect ENM properties, potentially yielding products with differing toxicity profiles. Further, pH changes in the small intestine, mucus, and resident microbiota in the GIT lumen add to the complexity (Bouwmeester et al., 2018). Various models are available that closely simulate human physiology and have been used for decades to assess the solubility, digestion, and epithelial permeability of conventional food and drug components in the stomach, small intestine, and colon. These models are now being explored and used for the assessment of food-relevant nano materials (NMs) (Lefebre et al., 2015; Braakhuis et al., 2015). In the end, a combination or battery of models may be required depending on the data gaps addressed. An example approach for assessing NM uptake in the gastrointestinal tract was proposed earlier in this chapter. This included a tiered testing strategy with a thorough physical and chemical characterization of the NM in the matrix as dosed to the test system. In such testing, it is important to assess NM stability, taking into account that NM changes over time are heavily influence by the local environment of the NM (i.e., the matrix). Following this physical and chemical characterization, toxicological characterization of NM should be initiated by using alternative testing strategies (in vitro or in silico). Ultimately, this would prioritize materials for further testing in vivo (EFSA, 2018).

The suitability of studies to underpin a risk assessment, however, is still disputable, severely limiting the use of this information for risk assessment purposes (EFSA 2009). Usually, the quality of nanomaterial characterization is the limiting component. For example, in most studies only a single sized, poorly characterized nanoparticle is used or nanoparticles are administered at unrealistically high doses, or a narrow range of effects are generally studied (Oberdorster et al., 2007b). In addition, when evaluating the plethora of in vitro studies with nanoparticles, caution has to be exercised when extrapolating their results or mechanisms for the hazard characterization to subsequent human risk assessment (Oberdorster et al., 2007b). The in vitro studies might be suitable for searching mechanistic explanations of toxic effects, or as screening methods in combination with profiling studies in a tiered hazard assessment approach (Balbus et al., 2007; Lewinski et al., 2008).

One of the most important questions for the safety assessment is the sensitivity and validity of currently used test assays. While the knowledge on potential toxicity of nanoparticles is growing, so far only studies following acute (single dose) oral exposure are available. There is a great demand for studies using chronic oral exposure to nanoparticles combined with a broad screen for potential effects. Information from toxicity studies with other routes of exposure indicates that several systemic effects on different organ systems may occur after long-term exposure to nanoparticles, including the immune, inflammatory, and cardiovascular system. Effects on the immune and inflammatory systems may include oxidative stress and/or activation of proinflammatory cytokines in the lungs, liver, heart, and brain. Effects on the cardiovascular system may include prothrombotic effects and adverse effects on the cardiac function (acute myocardial infarction and adverse effects on the heart rate). Furthermore, genotoxicity, and possible carcinogenesis and teratogenicity may occur, but no data on the latter are available as yet (Bouwmeester et al., 2009).

16.4.5 Characteristics and behavior of nanoparticles in food

According to the Woodrow Wilson Center's Project on Emerging Nanotechnologies, 118 consumer products from the food and beverage sector are currently available on the market at the time of writing this chapter (Project on Emerging Nanotechnologies, 2018). The list contains a range of items that come in direct contact with food, such as from aluminum foil or antibacterial kitchenware, but also dietary supplements (i.e., Nanoceuticals Artichoke Nanoclusters) or canola oil fortified with free phytosterols. Such products allow, directly or indirectly, nanoparticles to enter the human body via ingestion.

Engineered nanoparticles in food may encompass many forms. Here the focus will be on persistent nanoparticles, i.e., nonsoluble or biodegradable particles, since potential risks are predominantly associated with these types of particles. It is

likely that nanoparticles are used in foods in an agglomerated form, but it cannot be excluded that these agglomerates will break down and that the consumer will finally be exposed to free nanoparticles. Due to their specific chemico-physical properties, it is to be expected that nanoparticles could interact with proteins, lipids, carbohydrates, nucleic acids, ions, minerals, and water in food, feed, and biological tissues. Experimental data available so far indicate that the characteristics of nanoparticles are likely to influence their absorption, metabolism, distribution, and excretion (ADME) (Ballou et al., 2004; des Rieux et al., 2006; Florence, 2005; Jani et al., 1990; Roszek et al., 2005; Singh et al., 2006). For nanoparticles present in food, their interactions with proteins are important (Linse et al., 2007; Lynch and Dawson, 2008). Protein adsorption to engineered nanomaterials may enhance membrane crossing and cellular penetration (John et al., 2001, 2003; Pante and Kann, 2002). Furthermore, interaction with engineered nanomaterials may affect the tertiary structure of a protein, resulting in malfunctioning (Lynch et al., 2006). Therefore, it is important that the effects and interactions of nanoparticles are characterized in the relevant food matrix (Oberdörster et al., 2005b; Powers et al., 2006; The Royal Society and the Royal Academy of Engineering, 2004).

Translocation of particles through the gastrointestinal wall is a multistep process, involving diffusion through the mucus lining the gut wall, contact with enterocytes or M-Cells, cellular or paracellular transport, and posttranslocation events (des Rieux et al., 2006; Hoet et al., 2004). After passage of the intestinal epithelium, nanoparticles can enter the capillaries and enter the portal circulation to the liver, a major site for metabolism, or they can enter the lymphatic system which empties directly into the systemic blood circulation. The interactions with blood components might itself affect the fate of the nanoparticles. Unfortunately, there is little information regarding the distribution of nanoparticles following oral exposure (Hagens et al., 2007). But following other exposure routes, a widespread distribution of nanoparticles has been identified, where as a general pattern it appears that the smallest nanoparticles have the most widespread distribution (De Jong et al., 2008; Hillery et al., 1994; Hillyer and Albrecht, 2001; Hoet et al., 2004; Jani et al., 1990). Information on the potential of the nanoparticles to cross natural barriers like cellular, blood−brain, placenta, and blood−milk barriers is important for the safety assessors.

Very little is known regarding biotransformation of nanoparticles after oral administration. The metabolism of nanoparticles should depend, among other properties, on their surface chemical composition. Polymeric nanoparticles can be designed to be biodegradable. For metal and metal oxide nanoparticles, the slow dissolution will be of importance. Even less is known about the excretion of nanoparticles. As indicated, the potency of nanoparticles to interact with normal food constituents has raised speculation whether some nanoparticles may act as carriers (a “Trojan horse” effect) of contaminants or foreign substances present in food (Shipley et al., 2008). This could result in aberrant exposure to these compounds, with severe implications on consumer health.

Generally, the focus is placed on nonsoluble free nanoparticles. But another category of nanotechnology applications in food is represented by nanoencapsulates. These are specially designed to deliver their content with increased bioavailability. This type of application also needs to be considered by safety assessors.

To perform a robust safety assessment, more information needs to be gathered on the mechanism of ADME of nanoparticles and other nanostructures. Only when this information is available it will be possible to initiate extrapolation and modeling approaches that will allow a more generalized safety assessment of nanostructured particles in food. Due to the potential impact of toxicological effects, special attention needs to be paid to the possibility that certain nanoparticles can cross the barriers (e.g., gastrointestinal barrier, cellular barrier, blood−brain barrier, placenta barrier, blood−milk barrier).

16.5 Future developments and challenges

At the first International Food Nanotechnology Conference organized by the Institute of Food Technologists (IFT) in 2006, participants agreed that nanotechnology is still in its infancy, with food applications being rather in a preinfancy state, but also recognized a great amount of enthusiasm and anticipation surrounding this technology (Bugusu et al., 2006). Consumer acceptance and the regulatory issues will dominate and dictate its growth. In the absence of mandatory product labeling anywhere in the world, it is not easy to pinpoint exactly how many commercial products now contain nano ingredients. It is clear that applications of nanotechnology such as sensors or process innovations have very different risk profiles than those where nanostructures are added to food products and are ingested by the consumer. Likewise, applications where nanotechnology is used to improve certain properties of the packaging material of food products should be considered differently. The nanomaterial first has to migrate from the packaging material into the foodstuff and in the absences of migration consumers will not be affected. Of course also these applications need to be assessed for possible unexpected effects, but the impact will be different than in the case of nanomaterials directly added to food products. The type of governance of applications of nanotechnologies in food and food industry should be dependent on the type of application of nanotechnologies.

Although potential beneficial effects of nanotechnologies are generally well described, the potential (eco)toxicological effects and impacts of nanoparticles have so far received little attention. The high speed of introduction of nanoparticle-based consumer products observed nowadays urges the need to generate a better understanding of the potential negative impacts that nanoparticles may have on biological systems. The main concerns stem from the lack of knowledge about the potential effects and impacts of nano-sized materials on human health and the environment (Bouwmeester et al., 2009). In addition to the scientific risk assessment–related concerns, the consumers concerns regarding nanotechnology application in food products are mainly related to safety issues. It is recognized that the public concerns about the safety of products derived from new technologies may differ from those using established technologies (Siegrist et al., 2008).

Nanotechnologies used to improve certain properties of food products can range from the use of so called soft nanomaterials like micelles and vesicles to encapsulate nutrients and deliver them to specific locations in the gastrointestinal tract, to the use of nano formulated substances to improve the flow behavior of powdered foodstuffs. It is generally agreed among toxicologists that the supramolecular structures that are designed to break down within the gastrointestinal tract constitute relatively low risks, assuming that the molecules used to make these structures are safe. Also, nanoparticles that easily dissolve in water or are biodegradable will most likely not be very hazardous. Most of the concerns of applications of nanotechnologies in food are focused on nonsoluble free and persistent nanoparticles that potentially can pass certain barriers and enter the body, and subsequently enter certain tissues or even individual cells. Because of their persistent nature, they can stay there for prolonged periods and induce harmful effects. A special cause of concern is represented by nanoformulations designed to increase the bioavailability of the bulk equivalent. This might impact on the toxic profile of these compounds and needs to be assessed. To ensure that consumers are not subjected to unacceptable risks and that foods that incorporate nanotechnology products are as safe as those foods that do not contain nanomaterials, governance should focus on nonsoluble free manmade nanomaterials that have functional characteristics different from their bulk equivalents in food products.

The general public strongly associates nanotechnology with nanoparticles and therefore assumes that the risks of all applications of nanotechnologies are comparable with the risks of nonsoluble free nanoparticles. Since nanotechnology is an enabling technology, the actual form in which the consumer is exposed to the products of nanotechnology can be wide ranging. It is therefore important to educate the public and help it distinguish between the various forms and uses of nanotechnology, as well as the differences in risks between these applications. Unfortunately, the application of other state-of-the-art technologies in the past has shown that it takes time for this type of information to become widely accepted in society.

Proper regulation and monitoring of nanotechnology can help this process, since it would help build trust among users. Regulation implies that at least one impartial and objective body has reviewed and analyzed the specific application of the technology and has concluded that it is safe.

Globally, the scientific and industry communities need to come together to resolve the key issues of safety and public perception of nanotechnology. To fully exploit the benefits of nanomaterials without exposing the public to harm requires a judicious risk analysis and management. For the benefit of the humanity at large, the most expedient and efficient way of doing it is through global harmonization of the regulations of nanomaterials.

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