Benefits and Challenges of the Application of Nanotechnology to Food

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ABSTRACT

The number of potential uses of science and/or technology at the nanoscale level in the food and food ingredient industry is growing rapidly with ongoing research in a variety of application areas. Many applications offer considerable benefit to consumers in terms of product safety and quality. Testing protocols and guidelines for demonstration of the safety of food and food-related products, such as food packaging or food processing aids, need to be established (i.e., science-based policy and regulations) and communicated in consumer-friendly language. A possible strategy or decision tree for establishing guidelines for safety testing will be presented. The goal of this presentation is to generate dialog between the food industry, academic researchers, policy makers, regulatory scientists and consumers resulting in clearer understanding of the potential benefits and risks of nano-structured materials in food and to identify research needs and priorities for all stakeholders.

Keywords: food, consumer benefits, regulatory strategy

1 INTRODUCTION

The number of potential uses of science and/or technology at the nanoscale level in the food and food ingredient industry is growing rapidly with ongoing research in a variety of application areas. Many applications offer considerable benefit to consumers in terms of product safety and product quality.

2 NANOSCALE MATERIALS IN FOOD AND FOOD PRODUCTION

2.1 Naturally occurring nanomaterials in foods

Recent reviews of the safety of nanomaterials have stated that there is little information on oral exposure of humans to nanoparticles [1;2]. This generalized statement is not completely correct. We have been exposed to naturally occurring nanomaterials from our first day of life through food sources such as milk, including human milk and colostrum [3]. The nanosized components in milk include casein micelles (50-300 nm) [4], whey proteins (4-6 nm), lactose (0.5 nm) and fat globules (300 nm)[3;5]. Lomer *et al*. [6]reviewed dietary sources of and exposure to ultrafine (<100nm) and fine (0.1-1.0 µm) particles. Sources include foods containing titanium dioxide, aluminosilicates, and food additives. The daily intake of fine and ultrafine particles was estimated to be $>10^{12}$ particles/day [6]. Thus, we have a long history of oral exposure to nanoparticles and can be certain that it is possible for nanomaterials to be orally consumed with no adverse consequence.

The effect of engineered nanomaterials on the gastrointestinal tract has been evaluated using tracer nano-sized materials created for nutrition studies to further our understanding of lipid and fat-soluble vitamin absorption [7-9]. Studies with parental nutrition preparations have also evaluated the effect of particle size on absorption and digestion [10]. The self-assembly phenomena of nanoparticles has also been studied with food lipids [11]. However, we now have the capability to design nanomaterials with unique shapes and heterogeneous compositions that we have not been previously exposed to, and thus research on their safety is needed. This base of knowledge and experimental protocols from food and nutrition research may be useful for future studies on safety evaluation of novel nanomaterials.

2.2 Potential applications of structured nanomaterials in foods

There is great potential for consumer benefits of the use of structured molecules at the nanoscale [12]. These include, but are not limited to, improved delivery mechanisms for nutrients (e.g. fat-soluble vitamins) and other functional ingredients (e.g. flavors); improved food safety and biosecurity (e.g. enhanced microbiological stability); smart packaging, and sensors which can be used to detect possible problems with food quality and safety); improved packaging performance; and improved food processing.

For example, antimicrobials suffering from low activity in complex food systems due to partitioning in non-aqueous phases adsorption at interfaces or binding to food constituents such as proteins and carbohydrates have been the target of nanoencapsulation strategies. Incorporation in surfactant micelles, phospholipid vesicles, biopolymeric nanoparticles and nanostructured solid lipid particles has shown to either increase the activity of the antimicrobials against foodborne pathogens or spoilage organisms or

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extend the duration of the inhibitory activity of the active compounds [13].

These systems are also under increasing investigation to develop functional foods that are able to combat the increases in chronic diseases such as obesity, cardiovascular disease, hypertension and cancer. The inclusion of bioactive compounds that have shown to exhibit physiological beneficial effects upon ingestion in complex foods has proven to be challenging. Bioavailability of many compounds once incorporated in a food matrix are typically low because the compounds are often not be stable during processing and the compounds again physically and chemically interact with the multicomponent, multiphase food matrix. Nanoencapsulation of carotenoids, phytosterols, ? -3 fatty acids and other active compounds can greatly increase the fraction of the administered bioactive compound that reaches the systemic circulation and thus impart significant health benefits as a result.

3 SAFETY OF FOOD NANOMATERIALS

Food is an integral and necessary part of every consumer's life; however, the food industry faces unique challenges regarding the concern for safety of their products. The consequence of consumer misinformation and misunderstanding of the application of new technology to food resulting in exaggerated risk perception has been clearly demonstrated by consumer rejection of irradiated foods and biotechnology. This is despite the acceptance of use of these technologies by other fields, e.g., medicine. Therefore, it is imperative that testing protocols and guidelines for demonstration of the safety of food and food-related products, such as food packaging or food processing aids, be established (i.e., science-based policy and regulations) and communicated in consumer-friendly language. Such guidelines will help to provide a clear path for adoption and development of applications of this technology within the industry, plus establish consumer confidence that a proactive and transparent approach is in place to assure food products are safe to both consumers and the environment.

3.1 Need for safety guidelines

There are several reasons why the need for safety guidelines for food-related nanomaterials is becoming urgent. Firstly, the dissemination of non-specific warnings of hazards of nanomaterials to consumers by various consumer groups is well underway [14]. Proponents of mandatory labeling of products containing nanomaterials are spreading the message that anything nanosized represents a hazard. Thus, consumer misconceptions are being formed. Secondly, the lack of specific guidelines for data needs is already limiting the usefulness of research that is being conducted and published. Without adequate characterization of the tested nanomaterials, interpretation of the biological effects of those materials is very difficult to interpret and to extrapolate to other materials. Thirdly, industry is reluctant to invest in technology where there is perceived uncertainty of regulatory agency acceptance.

3.2 Safety decision tree strategy or weight of evidence approach to food nanomaterials

The goal of this presentation is to begin to formulate a strategy for establishing guidelines for safety testing of novel nanomaterials that will be used in food and food-related products. Approaches to food safety evaluation include a safety decision tree strategy [15] and the overall weight of evidence approach [16]. The weight of evidence approach is used by several food authorities (WHO, EFSA, FDA) for food safety evaluation, as this method takes into account all data on a particular compound before coming to a final conclusion. An essential part of the evaluation is recognizing and dealing with data gaps, uncertainties and assumptions, as essential elements of the risk assessments. This approach also allows for consideration of atypical observations that are difficult to incorporate into or predict for decision trees.

The data that will be required for evaluation of food nanomaterials should take into consideration the following factors: (1) the size and composition of nanomaterials being employed (i.e., metals, proteins, etc.); (2) the form of the nanomaterial (i.e., particles, laminates, composites, and other macromolecular networks); and (3) likeliness of exposure (i.e., food ingredient, food packaging, processing aid, etc.).

3.2.1. Size, composition and matrix: The characterization of nanoparticles is critically important. Factors that must be established include: purity (contaminants of nanoparticles have been associated with toxicity), size distribution (a 2 nm difference in size can affect the clearance pathway), and consistency of size (from lot to lot). Oberdorster *et al.* [17] have recommended 17 parameters of nanomaterials that are needed for safety evaluation. One of the challenges for the food industry is cost of characterization of nanomaterials and access to the scientific equipment.
The greatest safety concern for nanomaterials is with free nanoparticles [18]. Thus, the matrices in which nanoparticles are introduced may also be important.

3.2.2. Likeliness of exposure –
The data needs for safety evaluation of food applications of nanomaterials should take into consideration the likeliness of exposure to the materials. The FDA currently uses such an approach in the regulation of food packaging materials. If as if the manufacturer can document that the compound in question will not migrate from the packaging materials to the food, then extensive safety data is not needed. Similarly, whether the nanomaterial will be used directly in the food

product, which food products, at what levels and/or in the manufacturing environment will impact possible exposures.

3.3 Establishing testing guidelines

The challenge of establishing testing guidelines and protocols for nanomaterials has been addressed by several groups. These include the National Toxicology Program (http://ntp.niehs.nih.gov/files/NanoToxWorkshop.pdf), the National Cancer Institute's Nanotechnology Characterization Laboratory (http://ncl.cancer.gov/working_assay-cascade.asp), the Woodrow Wilson Center (http://www.nanotechproject.org/reports), and the International Life Sciences Institute (ILSI) [17].

3.3.1. Absorption and distribution: A change in size and/or solubility result in improved bioavailability of nutrients [8] and other potentially beneficial compounds in foods such as carotenoids [19]. This raises challenges as well as opportunities. The opportunities include fortification of food with reduced cost and enhanced benefits from nutraceuticals. The challenges include possible over-consumption of compounds due to greater uptake, and issues for nutrient labeling. Will the current guidelines for the amount of a nutrient to provide a given percent daily values need to be changed depending on the form of the nutrient? This is not a futuristic question as there are already dietary supplements in the market for nutrients claiming to be nanomaterials and therefore having a ten-fold increase in bioavailability [20].

The ability of specific engineered nanoparticles to cross a variety of physiological barriers, such as cell membranes, tight junctions between cells, and the blood brain barrier allows for a much greater distribution of the materials in the body. However, most of the data is based on inhalation exposure [1;18]. There is much less data on the ability of engineered nanoparticles to cross the mucosal lining of the gastrointestinal tract, although this is an area of investigation for improved delivery of various drugs. In one study, the distribution of ultrafine radioactive Ir particles following inhalation, gavage and intravenous exposure was compared using two different sizes of particles (15 nm and 80 nm) [21]. These studies demonstrated that while translocation of nanoparticles to other organs occurred following inhalation exposure, they were nondetectable in any tissue or urine and completely recovered in feces following oral exposure. Thus, the absorption and distribution, and ultimate safety, of nanomaterials via oral exposure cannot be predicted from inhalation studies.

3.3.2. *In vitro* assays for gastrointestinal uptake
A recent proposed strategy for evaluation of nanomaterials listed *in vivo* methods as the first tier for testing effects of oral exposure [17]. However, the fields of nutrition and pharmacology have established accepted *in vitro* methods for evaluation of gastrointestinal absorption, including gastrointestinal cell models such as CaCO cells and *in situ* gastrointestinal loop assays. In addition, *in vitro* models of digestion may be useful to assess the effect of digestion on food nanocomponents. It would seem that these model systems could be used as a first tier approach, to determine whether absorption of engineered nanomaterials occurs or not. If the nanomaterial is not absorbed and is not cytotoxic to the gastrointestinal tract, expensive *in vivo* testing may not be necessary.

3.3.3. *In vivo* testing methods
More dialog is needed to establish the protocols and endpoints that are appropriate for *in vivo* testing of food nanomaterials. Challenges include dose metric issues, the need for large amounts of materials for feeding studies, and appropriate delivery methods as the food-feed matrix should if possible, closely represent the exposure scenario for the nanomaterials.

3.3.4. Evaluation of benefits of nanomaterials
The promotion or claims of benefits of nanomaterials in consumer products should be accompanied with evidence that those benefits do exist. Discussion regarding what evidence is needed to demonstrate such benefits would also be helpful in maintaining consumer confidence in this technology.

Such information is needed by the industry to allow for the prediction of the ultimate cost of product innovation and introduction to the marketplace. As food is a low profit margin industry, the cost of safety testing represents a significant hurdle in new product development. Thus, to facilitate introduction of this technology within the food industry, regulatory data expectations must be understood.

4 SUMMARY

In summary, the unique challenges and opportunities that nanotechnology offers to the food industry and the resulting potential societal benefits that this may yield will be discussed along with the challenges and needs of industry. The goal of this presentation is generation of dialog between the food industry, academic researchers, policy makers, regulatory scientists and consumers resulting in clearer understanding of the research needs and priorities for all stakeholders.

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