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State of the safety assessment and current use of nanomaterials in food and food production

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Nanomaterials are developed for and applied in food, food additives, supplements and food contact materials. In an inventory of internet databases 140 products in the food and food-related sectors were identified that claim to contain nanomaterials. A great diversity of nanomaterials is applied, ranging from inorganic metal and metal oxides to organic nanomaterials that carry bioactive ingredients. Here we present an overview of nanomaterial applications that are currently available, discuss state of the art analytical chemical characterization and toxicological assessment methods, as well as categorization methods to support the safety evaluation of the application of nanomaterials throughout food production.

Introduction

Nanomaterials have unique functional properties that are mainly size related i.e. due to the much larger surface to mass ratio compared to the larger-sized bulk materials. Because of the unique functional properties of nanomaterials they are being used by many industries, including the food and agricultural sectors, and an increasing number of products that contain nanomaterials can already be found on the market (Chaudhry *et al*., 2008; Durán & Marcato, 2013; Nanotechnologies; Weiss, Takhistov, & McClements, 2006). The main drivers behind the application of nanosized ingredients and additives in food and food-related products are directed to improving food production processes, extending the shelf-life of fresh products, improving the consistency, stability and texture of products, and enhancing the uptake and bioavailability of nutrients. Nanomaterials could have a substantial impact on the food sector in the future, potentially offering benefits for industry and the consumer, although the specific properties and characteristics of nanomaterials need to be considered for any potential health risks.

Companies and institutes worldwide are currently studying and developing nanomaterial applications to improve or replace pesticides and antibiotics in agricultural food production, to modify the mechanical and sensorial properties of food, increase the nutritional value of food (Alejandro & Rubiales, 2009; Perlatti *et al*., 2012; Shi, Xu, Feng, & Wang, 2006; Verma, Singh, & Vikas, 2012). In fact, possible applications of nanotechnology can be identified in the complete food production chain. It should be noted that some substances have always contained nanoscale particles but have not been recognized as such. Fatty acid liposomes used in health products are another form of conventional substances that occur in nanosized micelle form. Proteins or protein micelles in many products have sizes that bring them into the nano-range. For instance casein, a natural protein in milk, spontaneously forms clusters and micelles with sizes ranging from 2 to 200 nm (de Kruif & Huppertz, 2012). In this paper we are concerned with engineered nanomaterials, mostly metal and metal oxide nanoparticles, and lipid-, carbohydrate- and protein-based nano-encapsulates in food, food packaging and supplements.

While the special properties of nanoparticles have led to innovative products, there are also concerns about their safety, especially because of our still limited knowledge of human health effects of these materials. In response to this uncertainty more up-to-date information is required on the state-of-the-art of applications of nanotechnology as pesticides, food additives, food contact materials and feed additives, i.e. the use of nanoparticles in the

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agricultural, feed and food sector. In this review, we will briefly discuss the currently used definitions of nanoparticles, and its applicability for food and the food-related sectors. In order to frame the need for a safety assessment of nanoparticles in these domains we present an overview of nanoparticles containing products that are currently on the market. This overview of most applied nanoparticles and product matrix combinations will direct the requirements for experimental procedures to generate data for the safety assessment. Recent advances in analytical method development will be discussed in relation the human exposure data generation as well as in relation to advanced models for hazard assessment and characterization of nanoparticles in food and food-related products. Finally, categorization approaches are briefly discussed as a screening method for safety assessment as long as adequate toxicological and analytical methods are not in place.

Definitions of nanoparticles

Nanotechnology is defined by the International Organization for Standardization as the "application of scientific knowledge to manipulate and control matter at the nanoscale in order to make use of size- and structure-dependent properties and phenomena, as distinct from those associated with individual atoms or molecules or with bulk materials" (ISO, 2010). The word "nano" refers to a billionth of a metre (10^{-9} m) and nanotechnology can be understood as the fabrication, characterization and manipulation of particles with sizes <100 nm (EFSA, 2011).

While nanoparticles, or nanomaterials consisting of such particles, are generally accepted as those with a particle size below 100 nm, this size limit is fairly arbitrary. The regulatory approaches addressing nanoparticles differ per region. In the USA, the FDA did not issue strict definitions of nanoparticles and considers food manufacturing processes that involve nanotechnology in the same manner as any other food manufacturing technology (FDA, 2011). The FDA recognizes that nanoparticles in food may have new properties and that additional or different testing methods may be necessary to assess the safety of the food substance. The variation in biological activity that may result from engineering food substances in the nanometre range may raise questions about the applicability of traditional safety tests for these materials. The FDA clearly states that, as with any studies to support the safety of food substances, studies to establish the safety of food substances manufactured using nanotechnology should have been appropriately validated for these materials (FDA, 2012). The same holds true for Europe, where in addition a proposal for a nanomaterial definition has been issued. The European Commission adopted the Recommendation on the definition of nanomaterials 2011/696/EU on 18 October 2011 (EC, 2011). According to this recommendation, a "nanomaterial" means:

- A natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, one or more external dimensions are in the size range 1 nm–100 nm.
- In specific cases and where warranted by concerns for the environment, health, safety or competitiveness the number size distribution threshold of 50% may be replaced by a threshold between 1 and 50%.
- By derogation from the above, fullerenes, graphene flakes and single wall carbon nanotubes with one or more external dimensions below 1 nm should be considered as nanomaterials.

It is expected that this definition will be used primarily to identify materials for which special provisions might apply (e.g. for risk assessment or ingredient labelling). However, there are various scientific and/or technical challenges related to the measurement of materials in the implementation of the recommended nanomaterial definition.

Apart from technical issues about the EU definition of a nanomaterial there is some discussion whether all particles smaller than 100 nm should be considered in this recommendation (Bleeker *et al.*, 2013). Legal labelling obligations and information requirements may require further specification to separate natural, incidental and manufactured nanoparticles (natural nanoparticles being materials that are already present in many food and feed products like for instance casein proteins in milk products); differentiate between soluble and non-soluble nanoparticles (materials in which nano-specific risks are limited because they dissolve quickly in media changing into non-nanoparticles), and organic and inorganic nanoparticles (soft nanoparticles being materials such as micelles, emulsions and liposomes for which nano-related risks are negligible, for example in case they fall apart in the gastrointestinal tract). Furthermore, new directions may be required for nanoparticles with a history of use. These are materials which are already on the market for a long time, whereas the authorization of these materials may be based on a dossier that is not suitable to investigate nano-related properties and/or effects. This may be the case for a number of current food additives as synthetic amorphous silica (SAS, E551) and titanium dioxide (TiO_2, E171), and materials that have a history of use in their colloidal form, such as silver.

Applications of nanoparticles in food and food-related products

Nanoparticles are used in food and agriculture in several application domains. In the primary production (agriculture) nano-formulated pesticides, fertilizers and other agrochemicals are being developed. The application of nanoparticles has also enabled the development of innovative packaging materials that can improve the safety and