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Overview on the safety of commercial products containing metallic nanoparticles in the food sector

Seguridad de los productos comerciales que contienen nanopartículas metálicas en el sector alimentario

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Abstract

The objective of this work was to highlight the importance of testing in a realistic way, metallic nanoparticles-based products, used in the food sector in order to provide representative data for a realistic and accurate risk assessment. To this end we give a brief overview of the current use and applications of metallic nanoparticles in the food industry, how the toxicological evaluations of nanoparticles in food should be performed and how nanoparticles-based products are regulated worldwide.

This brief overview work provides a picture of the latest issues on the safety evaluation of metallic nanoparticles in the food sector and identifies also some major points that are important to take into consideration for future studies.

Key words:

Nanoparticles. Food. Toxicity.

Resumen

El objetivo de este trabajo fue resaltar la importancia de analizar de forma realista los productos que contienen nanopartículas metálicas utilizados en el sector alimentario a fin de proporcionar datos representativos para una evaluación de riesgos realista y precisa. Con este fin, presentamos una breve descripción del uso y de las aplicaciones actuales de las nanopartículas metálicas en la industria alimentaria, cómo deben realizarse sus evaluaciones toxicológicas en los alimentos y cómo están regulados los productos de nanopartículas a nivel internacional.

Este breve trabajo general proporciona una visión de los problemas más actuales sobre la evaluación de la seguridad de las nanopartículas metálicas en el sector alimentario e identifica también algunos puntos importantes a tener en cuenta para futuros estudios.

Palabras clave:

Nanopartículas. Alimentos. Toxicidad.

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INTRODUCTION

A high number of studies on the application of nanotechnology to the food sector have been performed over the past decade (1). The great benefits that these technologies have generated, or have the potential to generate, have been established and at the same time concern for their safety has been considered. Similarly to the case of genetically modified organisms, food products based on nanoparticles have not encountered a wide acceptance by the consumers.

In terms of safety there is a difference between biocompatible/biodegradable nanoparticles and persistent/inorganic ones, such as for example metallic nanoparticles. The latter, in fact, can easily accumulate in the human body causing serious health problems. Nevertheless, even in the case of nanoparticles developed using natural biodegradable substances, such as lipid nanoparticles for example, there is no certainty that they will be totally harmless as they might not maintain their original structure over time or once they are ingested (2). Moreover, an increased bioavailability of bioactive substances, which is a successful application of nanotechnology, might end up being toxic. To date only a very few number of studies have been carried out to test the safety of such type of nanoparticles (3).

Most of the investigations carried out on the safety of nanoparticles so far have been performed on standard molecules, specifically developed at laboratory level and/or on developing products. Those studies are very important as they allow the safe design of nanoparticles for consumer products. However, in the past few years it has become clear that the toxicological characterization of nanoparticles is indeed a complex matter. Due to the changeable and complex nature of these compounds, the effect produced on living organisms can vary in time and depending on the exposure conditions. For this reason, their properties and effect should be tested in a variety of conditions of use.

In this context the present work has the objective of highlighting the importance of testing in a realistic way nanoparticles based-products in order to provide representative data for a realistic and accurate risk assessment of these novel entities. This objective will be reached by presenting a brief overview of the current use and applications of metallic nanoparticles in the food industry and on how the toxicological evaluations of nanoparticles in food should be performed according to the most recent research results. Regulatory aspects will also be overviewed to provide an exhaustive picture of the latest issues on the safety evaluation of metallic nanoparticles in the food sector.

TYPE OF METALLIC NANOPARTICLES EMPLOYED AND STUDIED IN THE FOOD SECTOR

The majority of metallic nanoparticles used in the food sector are silver (Ag) and Titanium (as titanium dioxide, TiO_2). Silver is considered one of the most potent antiseptics, in Europe it is authorized as a food additive (E174) and its use as nanoparticle in the food industry is exploiting the increased antiseptic capability of its nano-size. At nano-size it is mainly used in the development of active food contact materials with antimicrobial properties or in the coating of food related utensils (4). Colloidal nanosilver is also produced as food supplement. This type of product is marketed mainly in the internet and is sold as a disinfectant of the human digestive tract. However, such claim has not been sustained by any experimental result, additionally, risk-benefit analysis data are currently not available (5).

Titanium is employed mainly as TiO_2 as a whitening pigment due to its high refractive index and resistance to discoloration. In the food sector it is employed as an additive in candies, sweets and chewing gums, white icing and chocolate, among others, and it is indicated as E171. Besides being used directly at the nano-size, TiO_2 used at the micro size may release a small percentage of nanoscale particles (6).

TOXICITY STUDIES

TOXIC EFFECTS OF METALLIC NANOPARTICLES AND MODE OF ACTION

The small size of nanoparticles might alter the physicochemical properties of a compound with respect to its bulk form. Nanoparticles in fact present an increased surface-to-volume ratio that leads to a stronger chemical reactivity in comparison to the bulk form. Depending on the size, particles can overcome physiological barriers and enter cells or tissues damaging them. Inflammation, immunological reactions, and production of oxidative stress are the major effects of nanoparticles exposure (see for example the work of De Matteis) (6). The toxicity of metallic nanoparticles is also due to the release of ions. As a matter of fact, there is a controversy in the literature concerning which of the two characteristics (size or ion release) is the real responsible for the toxicity of nanoparticles (5). Considering the studies performed so far it is very likely that both mechanisms are involved in the induction of toxic effects. Several works, in the case of colloidal nanosilver, have also reported the progressive release of ions from the bulk form establishing a so called Trojan horse effect of metallic nanoparticles (see for example Park *et al.* [8] and Bömert *et al.* [9]).

One of the most important finding of nanotoxicological studies has been the understanding that the effect produced by nanoparticles greatly depend on the prevailing chemical conditions present at the moment of testing. The physicochemical properties of nanoparticles can if fact change depending on the pH, the temperature, the presence of organic substances (5,9). This fact, on the one hand, justifies the controversial results obtained in the different nanotoxicological studies performed in the last decade; and on the other hand, has pushed the regulatory bodies in advising the performance of a physicochemical characterization of the compounds in different moments of the toxicity test as it will be shown further on.

TOXICOLOGY TESTING AND RISK ASSESSMENT PROCEDURES

Early toxicological studies on nanoparticles were performed using standard toxicological methods. However, due to the influence of the physicochemical characteristics of nanoparticles on their toxic effects, a full characterization considering parameters such as size, morphology, distribution, aggregation state, etc. by employing different techniques, soon started to be essential for the correct interpretation and comparison of toxicological studies. Such characterization was initially performed on the nanoparticles in their pristine state, *i.e.* as they came from the manufacturer. Further on, scientists realized the importance and the influence of the experimental conditions on nanoparticles characteristics and their toxic effect. As a matter of fact, the European Food Safety Authority (EFSA) Scientific Opinion entitled Guidance for risk assessment of engineered nanomaterials (10) has taken this issue in serious consideration and as the properties of nanoparticles may change in different environments, EFSA recommends examining the following conditions: 1) the state in which the nanomaterial was produced; 2) the state in which the nanomaterial is used or is present in the food and feed; 3) the state in which the nanomaterial is present in the toxicological studies and 4) the state of the nanomaterials in biological fluids and tissues. If the properties and behavior of nanoparticles are known and exposure is expected, potential hazards should be identified. Finally, *in vitro* genotoxicity studies, toxicokinetic analyzes and a 90-day study in rodents with repeated oral administration should be used (10).

EFFECT OF METALLIC NANOPARTICLES IN THE DIGESTION PROCESS

One of the aspects of nanotoxicology, that has only been recently investigated, is the behavior of nanoparticles during the digestion process. The fact that nanoparticles effects are strongly influenced by the chemical conditions of the surrounding environment highlight the importance of this evaluation.

When passing through the gastrointestinal tract, nanoparticles are exposed to a variety of conditions (*i.e.* digestive juices with different pH and ionic strength, digestive enzymes) that can influence the behavior of the particles by altering properties such as size, shape, charge and aggregation. The presence of bile acids, fatty acids, enzymes besides decomposing the food can also alter the nano-size structure.

Depending on the physicochemical property of the nanoparticle, a complete dissolution of inorganic nanoparticles or aggregation into larger particles may occur (11) and at the same time the formation of new (see Bömert *et al.* and references therein) nanostructures from dissolved compounds in the gastrointestinal tract could appear (see Bömert *et al.* and references therein) (9). Silver nanoparticles, for example, have been shown to pass the digestion process in a nanoscale form but to undergo a strong transformation in their aggregation depending on the food ingested (11). Additionally, nanoparticles might produce a negative effect on the digestive process by inhibiting digestive enzymes, absorbing food components or by altering intestinal microbiota (9).

REGULATION ASPECTS

Market approval of consumer products containing nanoparticles must go through the demonstration of the safe use of such new products without posing risk to the consumer and the environment. Different approaches have been taken in regulating nano-based products in the agri-feed-food worldwide and, European Union (EU) and Switzerland are the only regions where nano-specific provisions have been incorporated in existing legislation. There is currently no legislation entirely dedicated to regulation of nanoparticles, neither in EU or elsewhere (12).

In the EU the use of nanotechnology in food is currently covered by European Commission (EC) regulation 258/97 concerning novel foods and novel food ingredients (1997). This regulation is currently under revision and the approval of novel foods consisting of engineered nanomaterials will take place from 2018. Substances added to food for a technological purpose or to improve solubility, flavor or bioavailability are covered by the food improvement agent package including various regulations such as that on food enzymes (1332/2008), additives (1333/2008) and flavorings (1334/2008). The use of nanoparticles as functional molecules, on the other hand, is covered by the regulation on food supplements (Dir 2002/46/EC). Separate regulation applies to nanoparticles used for food contact materials (1935/2004). Additionally, since December 2014, all nanoparticles in food must be identified by the word “nano” to inform consumers about the nano-scale of ingredients (13).

Regulation of food products containing nanoparticles is not harmonized worldwide. This might increase the risk for the consumers as some products that have not gone through a specific pre-market approval in EU can still be purchased in the internet.

CONCLUSIONS AND GENERAL REMARKS

From the brief overview presented it emerges that to assess the safety of nanoparticles in a realistic way is of paramount importance to perform an accurate physicochemical characterization over the entire toxicological assay to take into account possible changes that the nanoparticles might go through in different environments. Simulation of digestion situations should also be performed to dispose of a full picture of the effect of nanoparticles in food and after the digestion process. It is also relevant to increase the testing of real nanoparticles-based food products present in the market. Most toxicological characterization performed so far have in fact been performed at laboratory level without taking into proper consideration the effect of the matrix of the food, for example. It is also important to consider that the physicochemical properties of the products containing nanoparticles that are released in the market are not known. For this reason, an effort should be made to test such products. This is especially necessary

considering that the regulation of products containing nanoparticles in the food sector is not harmonized worldwide and some potentially toxic products might be accessible to the consumers via the internet.

Future research should also focus on determining the long-term effect of nanoparticles, establishing the effect of food matrix on nanoparticles toxicity, increasing the knowledge of the effect of nanoparticles on the human digestive tract and microbiome, and on performing epidemiological studies.

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