Journal of Chemical Science and Chemical Engineering
Volume 2 | Issue 1

Research Article Open Access

A Review: Metal Nanoparticles and their Safety Processing in Functional Foods

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Citation: Loutfy H. Madkour (2021) A Review: Metal Nanoparticles and their Safety Processing in Functional Foods. J Chem Sci Chem Engg 2(1): 19-37.

Received Date: April 07, 2021; **Accepted Date:** April 23, 2021; **Published Date:** April 27, 2021

Abstract

A Safety of nanotechnology in food industries has been discussed. Different nanomaterials (NMs) such as nanopowders, nanotubes, nano-fibers, quantum dots, and metal and metal-oxide nanoparticles are globally produced in large quantities due to their broad applicability in food-related industries. We present some uses of nanoparticles in food and related industries and their possible side effects. The various aspects of nanoparticles and their impact on human exposure, safety, and environmental concerns have been discussed. ZnO NPs are listed as a kind of safe substance by the FDA. The safety of nanostructured synthetic amorphous silica (SAS) as a food additive (E 551) has been discussed. and has always been produced by the same two production methods. Bioavailability increases for iron of nanometer size. The characteristics of broad spectrum of activity against food pathogens of silver nanostructures gives an insight for their potential applicability in incorporation of food packaging materials and antimicrobials for stored fruits and foods.

Keywords: Food-processing industry; Food safety; Nanostructured; Silicon dioxide; Silver nanostructures; ZnO NPs; Antimicrobial activity

Introduction

To make full use of nanotechnology in the food and related industries, we must have a thorough understanding of nanoparticles. Overall, this chapter indicates that nanotechnology has great potential for delivering herbal drugs and nutraceuticals, and in light of the comprehensive health problems, its utilization for effective disease prevention and health promotion is necessary and to be anticipated. Even though nanotechnology offers promisingapproaches in herbal drug delivery and nutraceutical applications, additional innovative research is needed to address the cost effective and long-term safety of the nanoparticles.

The arrival of nanotechnology in various industries has been so rapid and widespread because of its wide-ranging applications in our daily lives. Nutrition and food service is one of the biggest industries to be affected by nanotechnology in all areas, changing even the nature of food itself. Whether it's farming, food packaging, or the prevention of microbial contamination the major food industries have seen dramatic changes because of nanotechnology. Different nanomaterials such as nanopowders, nanotubes, nanofibers, quantum dots, and metal and metal-oxide nanoparticles are globally produced in large quantities due to their broad applicability in food-related industries. Because of the unique properties of nanostructures and nanomaterials – such as a large surface area, high activity, and small size, there is some concern about the potential for harmful adverse effects of used nanomaterials on health or the environment. However, because of tremendousadvances in different industries, this concern may be unnecessary. New nanomaterials make them more suitable for different applications in different industries. However, these materials may create threats of environment pollution or even harmful effects on human health [1-3]. Our knowledge regarding the safety of used nanomaterials in food and nutrition industries is low. Also, note that some nanomaterials enter the human body.

A report by the British Royal Society notes that we may face a nanotoxicitycrisis in the future.

Food nanotechnology is rapidly gaining attention in food science and industrial applications. Aspects related to legislation, general acceptance by the consumers as well as the development of fabrication methods to produce competitive nanofoods represent a challenge that has to be framed within a multi- and interdisciplinary scope. Foods are inherently nanostructured materials constituted by the self-assembly of thousands of compounds in different compartments and states of aggregation including amorphous, crystalline, vitreous, and rubbery which have the natural task in the living organism of inducing multiscale functions that are often onset at the nanolevel. FDA regulations [4], state that nanofood materials must have at least one dimension in the nanoscale range (1–100 nm), also establish that these products must exhibit properties and phenomena, including physical or chemical properties or biological effects that are attributable to its nanodimension(s). Therefore, particulate systems exhibiting sizes larger than 100 nm but possessing cracks, pores, cavities, etc., in the nanorange, which provide function to the food product such as immobilization of water promoting its preservation as well as of substances such as vitamins and minerals within these structures, are considered in the nanofood field.

There is a need to establishing exposure limits for the NP; however, the lack of adequate toxicological data is the main barrier to developing maximum worker exposure to most NP. The second barrier is the lack of standardized and validated methods to monitor the concentrations of NP in the workplace. Furthermore, the occupational benchmark is based on a standard atmosphere for non-nanosized fine particles. In the report by Gordon et al. [5], a group consensus failed to be reached on any of these points, but some recommendations were established such as the adoption of more effective hygiene measures to control occupational exposure to NP. There is also the need to implement quicker and more costeffective methods to evaluate the toxicity of the new NP. Also, we must create predictive models to correlate the response of NP by using *in vitro* and *in vivo* models in the short and medium term [5]

The number of innovative processes for manufacturing a vast number of nanoproducts is steadily growing such as those related to food preservation by nanostructured materials and by water mobility control as well as those involving novel hardware, tools, and interpretation algorithms directed to the design and preparation of commercially available nanoproducts and to those that are in the pipeline for patenting, and close to the mass production stage such as the vast number of dispersed systems that have been developed, additives, nanopackaging, food biosensors, and biomarkers. In addition, complex and highly specialized pieces of equipment used to produce and appraise these products have been developed in the last years and principles of the standards and regulations in this field are being discussed, including issues related to labeling and ambient-related constrictions and polluting hazards and disposal tasks.

Internet searching indicates that at present there are over 1300 identified nanoproducts that are produced by hundreds of different companies located in many countries, with the USA having the greatest number, a number that has more than quintupled over the past 10 years. Many of these products are available online from noncredited companies and may implicate a risk for the potential consumer.

Recent developments on nanosized materials have been developed in various food-related fields in different fields. In the food–agro sector [6], it is possible to mention, nanocapsules for the efficient delivery of pesticides, fertilizers, and other agrichemicals; delivery of growth hormone doses in a controlled fashion; nanoparticles for targeted genetic engineering and nanosensors for monitoring soil conditions and crop growth; nanocapsules to improve of nutraceuticals in standard ingredients; nanoencapsulated flavor enhancers; nanotubes and nanoparticles as gelation and thickening agents, nanoparticles bioavailability to selectively bind and remove chemicals or pathogens; nanoemulsions and nanoparticles improving absorption and distribution of nutrients; nanoencapsulation of nutraceuticals for better stability, delivery, and absorption; cellulose nanocrystal composites as nutrient carriers; coiled nanoparticles to efficiently deliver nutrients to cells without affecting color or taste and in food packaging developments including antibodies attached to fluorescent nanoparticles for detecting chemicals or foodborne pathogens; biodegradable nanosensors for temperature and moisture monitoring; and nanoclays and nanofilms as barrier materials to prevent spoilage, electrochemical nanosensors to detect ethylene, surface coatings with nanoparticles of Ag, Mg, Zn, and heatresistant films with silicate nanoparticles.

Evaluating nanomaterials in foods include three main aspects: definition of the type of nanomaterial, its relation to the process/product and appraisal of the end application [7]. Potential exposures' risks to nanomaterials include: nanosized or nanoencapsulated ingredients released in food processing, migration from food contact materials, residues from nanoformulated or nanoparticulate agrichemicals, contamination due to nanocompounds released to environment in such a way that the risk assessment and characterization there implies, the hazard identification and characterization, exposure assessment [8], and regarding physicochemical analysis decision scheme, it is heuristic in nature [7] and once a particular nanomaterial is analyzed for the first time, the methods may change and be more appropriate for the particular nanomaterial in the subsequent analyses until an established method is adopted.

Characterization of metal nanoparticles and its security in health

The main concern regarding human exposure to nanoparticles is that there are different entry routes such as digestion, inhalation, or skin absorption. After absorption, nanoparticles may enter the bloodstream and settle in different tissues such as the brain or trigger immune responses [2, 9]. These particles behave similarly to asbestos [10]. Some authors have studied genetic alteration as a potential consequence of nanoparticles in food or nanoengineering of food [11]. Some social and non-government organizations like Action Group on Erosion, Technology and Concentration (ETC Group) have called for a moratorium on the release of nanotechnology products until their safety has been demonstrated [12]. Despite all of these debates, nanotechnology has already entered into food packaging, agriculture technologies, and foodprocessing, as well as the nature of food, so the public is seeking safety assurances from governments and food producers [13].

Nanoparticles possess unique properties, so the marketing of nanoproducts is expanding. For example, in 2006, USD 20 billion in food industry products was devoted to nanotechnology [12], in agriculture and food processing. Proponents emphasize that this can improve the quality, nutritional value, safety, and quantity of food to meet the needs of a growing population [14, 15].

The developed NP has been grouped into four types: (1) materials based on carbon and fullerenes, such as shungita, i.e., the most stable carbon form; (2) materials that contain a metallic base such as titanium dioxide (TiO_2) and zinc oxide (ZnO); (3) dendrimers or polymers, such as polyamidoamine dendrimers and polypropyleneimine dendrimers; and (4) the composites of metals, such as platinum with silica cover and layers of Al_2O_3-TiO_2. Such materials have mainly been used by eight industrial areas: automotive, aerospace, electronic and computing, energy and environment, food and agriculture, construction, medicine and pharmacy, and personal care [16].

When the use of NP is applied to the production and supply chain of agrofoods, the properties of NP open up new ways to study and promote changes on intra- and intermolecular levels, besides generating catalysis and chemical reactions, muscle contractions, cell transportation, DNA replication, and transcription, among others [17]. All of these functions depend on the physicochemical characteristics of the particles such as their surface area, size, shape, zeta potential, and affinity for a number of different compounds forming the protein corona [18]. Such a layer modifies the physicochemical characteristics of primary NP and admits agglomerates whose surface reacts with the system in which the NP are dispersed and induce intracellular changes such as structure's modification, cellular cascade induction, and cell cycle deregulation among others. Consequently, before performing any study of NP toxicity, it is necessary to characterize them in the medium to be used (Fig. 1).

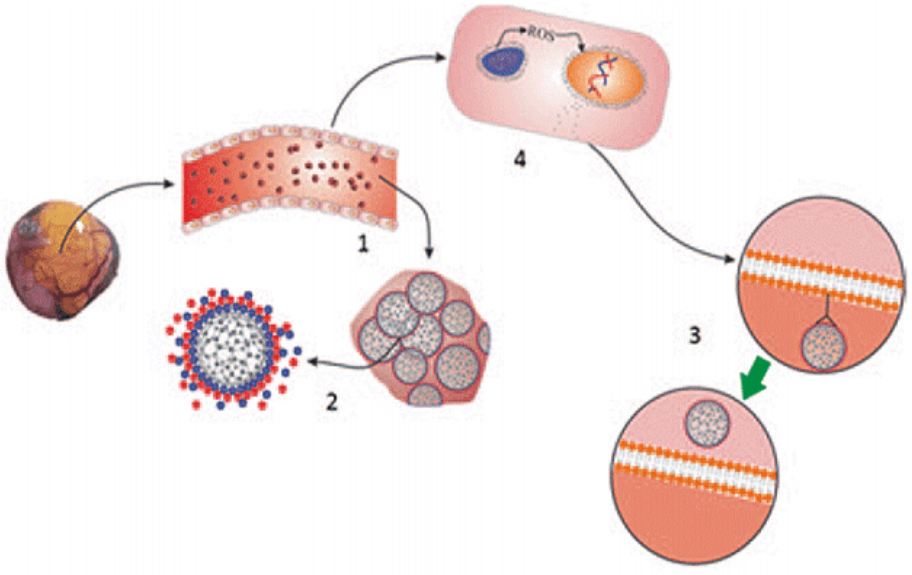

Figure 1: Model of endothelial NP internalization. **1** After exposure, for example, inhalation, dermic wound contact, or oral consumption, NP could reach the bloodstream and interact with blood components; **2** modifying NP properties such as charge, size, and zeta potential, among others; **3** some NP can be internalized by endothelial cells through receptors; and **4** after uptake, it can cause reactive oxygen species to increase and DNA damage.

The accelerated process of elaboration and the increase in use of the new NP have not allowed evaluating or predicting the environmental and human health risks. On the other hand, the exposition to these NP is increasing and tends to accumulate in a variety of systems like, for example, in the aquatic media, soil, air, plants and animals, and humans [19-22]. Due to the small size and big surface of the NP, the latter could penetrate the human cells, provoking diseases such as asthma, bronchoalveolar and cardiovascular disorders [23], Parkinson [24], Alzheimer [25], and cancer (IARC [26]), among others.

Exposition pathways of nanoparticles in humans

There are three pathways of exposure of NP for the latter to get into the human. One of them is inhalation in occupational settings, when the concentration of NP in the air is greater than the recommended by the National Institute for Occupational Safety and Health (NIOSH). The recommended concentration will depend on the type of NP to which it relates but is usually less than 10 g/m^3 . Another exposure pathway to NP is the dermal contact through the use of personal care products such as creams, toothpastes, and makeup, among other products containing NP. The third predominant pathway of exposure to NP inside the human is through ingestion of contaminated water or foods that contain within them or who had contact with the NP, such as in packaging [27].

Once they get into the human through inhalation, the NP form agglomerates of various sizes that can be deposited on the bronchoalveolar area, and if the NP agglomerates are small enough (< 25 nm), they can be translocated to the circulatory system [23]. On the other hand, if the NP agglomerates in cosmetics come by chance into contact on a skin wound, these NPs could also reach the bloodstream [28]. And finally, when NPs are orally ingested, the transport through the gastrointestinal (GI) tract deposits them in the small and thick intestine where, through microvilli, some of these NPs pass to the Peyer's patches and many others pass to the colon, which also has villi that allow the transport of the particles into the circulatory system as shown in Fig. 2 [29]. Some types of NPs which have been distributed through the blood vessels, liver, and lungs are able to penetrate cellular barriers such as the blood–brain and placental barriers [28]. In the case of mice, the immune cell profiles in response to a silver NP injection has been evaluated, and the authors concluded that the exposure can modulate the immune system in a dose-dependent mode, with smaller-size particles generating more severe effects [30]. The tissue distribution of NP depends on the physicochemical and morphological characteristics which could be associated with inflammation, atherosclerosis, tumor growth, and metastasis [31]; therefore, although it is known that NPs distribute and accumulate in the body, it is not easy to estimate the minimum time of exposure required to cause changes at the cellular and molecular levels, but there are recommendations on the time and exposure concentrations in each type of NP in particular. Such recommendations come from various institutes and agencies responsible for the security of NP in humans. For example, a recommended limit of exposure to the TiO_2 NP is 0.017 mg/m^3 [32], 0.3 mg/m^3 [33], and 1.2 mg/m^3 (NEDO 2009) but without establishing a clear limit of occupational exposure due to the impracticality of some measurement techniques, the lack of adequate toxicological data, and the uncertainty of dose or exposure measures in investigations, among others [5].

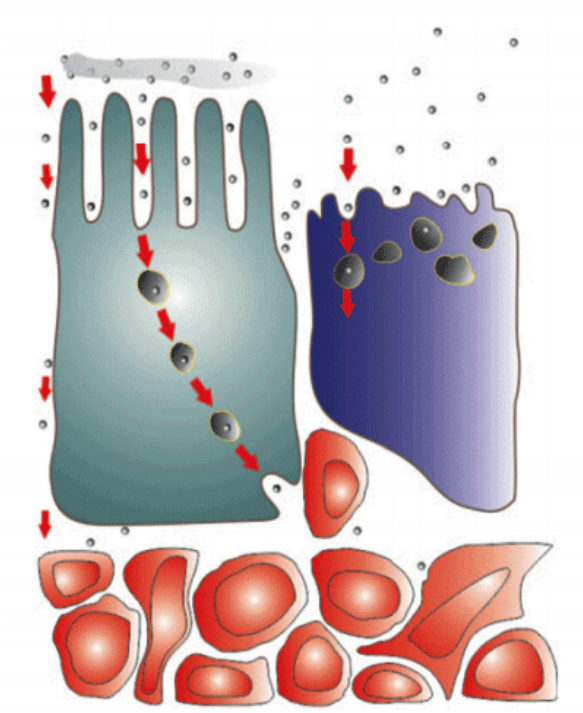

Figure 2: Entry of the NP from the microvilli of the intestine into the bloodstream. When the NP (gray spheres) orally reach the small and large intestines, they can enter the bloodstream by three paths: a through the microvilli (top fingerlike), b by crossing the cell junctions (spheres followed by small red arrows), making them loose (transitosis), and c by natural killer cells (thick red arrows) invaginated NP (gray spheres surrounded by black) until the NP enter the bloodstream (red area) and are distributed throughout the body

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The NP life cycle begins with manufacturing, continues with transport and processing, transport of the finished product, consumption by humans or other living organisms, and ends with recycling or disposal of NP or the products in which they are present [27]. Nanoparticles are not biodegradable and accumulating in the environment when they are unintentionally

released into environments dedicated to the production of human food commodities and water reservoirs. They may interact with the compounds of the ecosystem or consumed by organisms, thus causing a number of problems such as changes in the ecosystem or gene mutations [27]. Consciousness must be induced in the use and proper handling of NP, and international standards must be established for its regulation.

Safety uses of nanoparticles for food nutrition industrial applications

In food industries, the main priority is quality and safety of food, so health risk assessments in this area are essential. Since nanoparticles have entered food and related industries, toxicology research of nanoparticles is essential. Researchers in this area should pay special attention to the gastrointestinal absorption and possible side-effects of nanoparticles. Nanoparticles can have serious effects on health when they accumulate in high concentrations in tissues, eventually leading to tissue dysfunction or damage. With the increasing use of nanomaterials, concerns are also growing between experts but with increasing information of nanoparticles toxicity, public have not participate in this book. Perhaps the main reason for contradictory information on the toxicity of nanoparticles is in terms of characterization and tests [34]. Therefore it is necessary to establish standard protocols for risk assessment. Moreover, the difference between humans and laboratory animals prevents extrapolation of the results [35].

A complete understanding of the risks of nanomaterials in food industry requires improvements in at least three domains. First, methods must be developed because of the unique properties of nanoparticles. Conventional methods cannot be used in their case. Conventional methods like 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) or calcein AM (CAM) have not been useful for evaluation of toxicity in some nanostructures like single-wall carbon nanotubes (SWCNT), QD, fullerene, etc. It has been shown that SWCNT could interact with markers of this test [36]. It has been suggested that, in the case of nanomaterials, several methods for cytotoxic evaluations may be needed [36]. Following the fate of nanoparticles in humans or laboratory animals requires a precise characterization technique. Recently, specific analysis methods have been introduced to nanotoxicity evaluations [37].

Another area related to the use of nanoparticles in food and related industries is the absence of regular and systematic classification of used nanomaterials. The method of preparation and synthesis of nanoparticles in food products must also be classified and published. The absence of such classifications creates consume reluctance to use nanoproducts. In another scope, researchers must develop proper *in vitro* and *in vivo* models for toxicity assessment of used nanoparticles in food and related industries. It has been shown that *in vitro* models are not proper for pulmonary toxicity estimates of nanostructures [38]. Fig. 3 gives nanotechnology matrix in food industries.

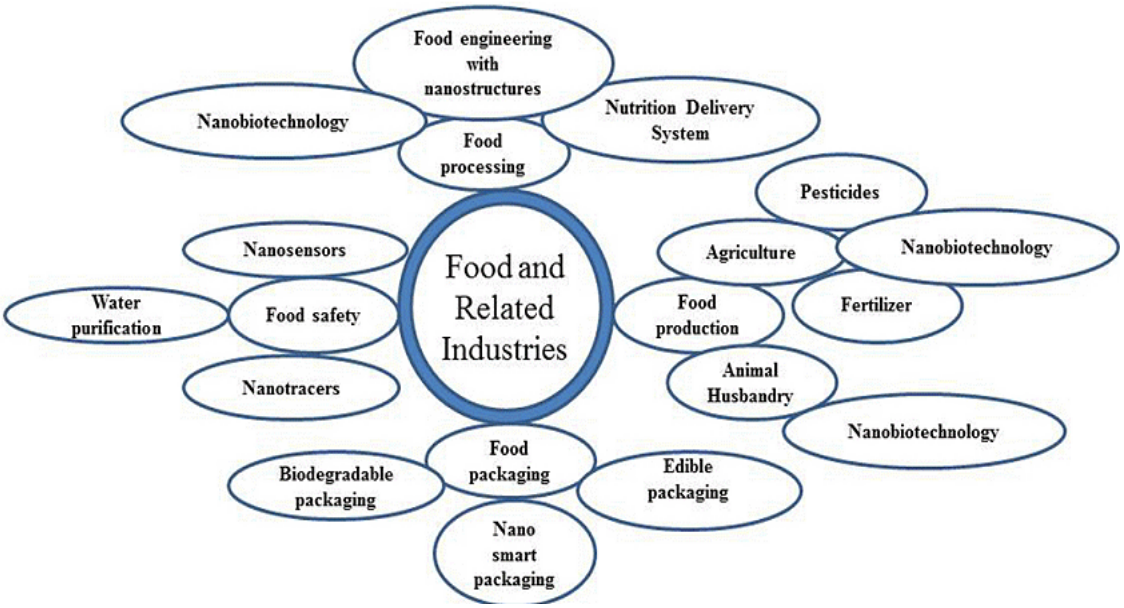

Figure 3: Nanotechnology matrix in food industries

Nanotechnology has focused on the packing, processing, quality, safety, and nutraceutical and functional properties of the additives directly in food, packaging materials, and food supplements [39], since the NP can be used as sensors for pollutants, antimicrobials, diffusion barriers, and changes in the nutritional quality of food, thus contributing to consumer safety [40-43]. However, there are technological and economic implications within agrifood systems when changing the work techniques, increasing the lifetime of the products, and preventing pest attack, among others [17]. It has been reported that there are about 200 companies worldwide involved in the processing of NP for food-related applications [44]. In Mexico, some of the companies related to NP usage are Sensient Colors, Tate & Lyle, Ingredion, BASF, DSM, Fortitech, FX Morales, MF Powers, Naturex, Palsgaard, DuPont, and Sensient Flavors.

However, it should be noted that despite the increased number of publication of food production-related NP patents and the rapid rise in products that contain them, there is still no scientific evidence that demonstrates that its consumption is safe for humans, and the research on the toxicity of NP has not been in proportion to their development. A review in SCOPUS, until mid2014, showed that while there are 2215 studies using the keyword "nanoparticles food," only 335 studies were reported using the keyword "food nanoparticles safety" and 35 studies using the keyword "food nanoparticles security." Therefore, although the use of nanotechnology has shown to favor the quality of foodstuffs, it must still be evaluated that these products do not threaten the integrity and health of consumers. Also, more emphasis is needed in the study of the risks and opportunities to avoid damaging the agricultural chain and not increasing the food prices [17].

4.1 Metal Oxides

The development and synthesis of NP such as titanium dioxide(TiO2), zinc oxide (ZnO), silicium oxide (SiO2), cupric oxide (CuO), cuprous oxide (Cu_2O), tin oxide(SnO_2), ferric oxide (Fe_2O_3),and cobalt oxide (Co_3O_4) have provided major advances in areassuch as mechanical, optical, electrical, and chemical, in addition to other uses in food. However, nowadays, there are few studies on the effects of metal oxide NP on human and environment in relation to the number of studies for the synthesis of NP.

Metal oxides and metals may, accidentally, be in contact with foods such as TiO2 (E 171), SiO_2 (E 551), Ag (E 174), ZnO (E6), and Co (E_3), because they are part of food ingredients, or not incidentally as SnO_2 and $Fe2O_3$, because they are acquired from the environment or through the packing materials or sensors.

4.2 Incidental and not incidental food additives

Incidental additives present in foods are due mainly to pesticides, herbicides, or chemicals which were in contact with the product during manufacturing or by contact with contaminated soil or containers used to transport food. On the other hand, not incidental additives are used to improve food quality.

4.2.1 Titanium dioxide (Tio_2 named as E 171)

TiO_2 NP is present in various products such as sunscreens, toothpastes, vinyl paints, makeup and cosmetics, as carrier of drugs and in foods such as milk, ice cream, water flavoring powders, mozzarella cheese, preserved sweets, and chewing gums, among others, thus favoring the consumption of 1–2 mg of TiO_2 NP/kg per day [45].

It has also been reported [45] that there are various diseases associated with oral exposure of the TiO_2 NP, such as gastritis, colitis, and Crohn's disease [46], but we have not found that these effects demonstrate under controlled conditions in vitro or *in vivo*. It has also been reported that TiO_2 NP has the ability to induce an increase in the expression of vascular endothelial growth factor (VEGF) [47]. VEGF, along with hypoxia inducible factor (HIF-1α), constitutes two of the most important factors involved in the process of generating new blood vessels from pre-existing vessels. This process is known as angiogenesis [48] and is usually involved in tumor formation. There are some in vivo and *in vitro* studies performed with anatase that evaluated the effects of TiO_2 NP on the skin and lungs; however, there are few studies performed with TiO_2 E 171 that evaluate their effects on the GI tract and circulatory system. FDA has also approved the use of the combination of SiO_2 and TiO_2 NP in food to aid the solubility of TiO_2 NP in the food media (FDA CFR73.575 21).

4.2.2 Silver zeolite (E 174) and silver nanostructures

The silver zeolite A is a silver zinc sodium ammonium alumino

silicate $M12(2AlO_2 \bullet 2SiO_2)6\bullet 27H_2O$ (with M = Na+, Ag+, Zn_2+, NH_4+). This compound (food grade) may have Ag contents above 5 % (w/w). The function of this substance is to preserve and control the growth of microorganisms in products. According to the demand, the silver zeolite A compound is not intended to have a technological effect in foods [49]. Besides, Ag NP are used in cosmetics, electronic items, clothing, paints, sunscreens, bactericides, and for medicalrelated purposes (dental crowns and cancer treatments, among others; [50]).

One concern on performing toxicological studies of NP is to know the effects when they are incorporated into the environment. In this regard, it has been shown that mobility, bioavailability, and toxicity of the NP of Ag are dominated by its colloidal stability in which the hydrodynamic diameter of the agglomerates of Ag NP had a dispersion of 27–42 nm and a zeta potential value varying from – 40 to – 46 mV when suspended in water [50].

In addition, studies were performed on protein corona covering Ag NP when the latter are suspended in different media, and it was found that the hydrodynamic diameter did not show significant

differences when suspended in water and in a culture medium [51]. However, the stability of the suspension decreased about 20 units. This is probably due to flocculation when in contact with biological environments.

Various *in vitro* studies have indicated that Ag NP is toxic to mammalian cells, cells derived from skin, liver, lungs, brain, vascular system, and reproductive organs [52]. It has been suggested that the toxicity was due to Trojan horse effects, when Ag+ ions are released into the aqueous media once Ag NP is solubilized in biological media [53]. It has been found that exposure to Ag NP was associated with increased ROS, release of cytochrome C into the cytosol, and translocation of Bax protein in the mitochondria [54]. It was also found that exposure of Ag NP by inducing p53 apoptosis pathway, whereby these NP are used in chemotherapy [16]. Also, it has been found that Ag NP can be translocated by blood circulation and can induce the destruction of the blood–brain barrier and neuronal degeneration [55]. Some immunological aspects were described before in this chapter [30]. Toxicological aspects of Ag NP were also evaluated by EFSA in 2005 [56]. In that study, it was reported that a person consumes up to 10 g of Ag NP orally. Based on this information, a restriction of 0.005 mg/kg food with Ag NP could limit the intake to less than 13 %. Thus, an adult of 60 kg of body weight could be exposed to 0.044 mg Al/kg/week [49].

Silver is ranked in the EFSA 3 Scientific Committee on Food (SCF) list, i.e., the group of additives for which there has not been established a daily intake recommendation, but their presence in food is accepted by restricting it to 0.05 mg Ag/kg food, based on the maximum concentration that causes no detectable adverse alterations in morphology, functional capacity, growth, development, or viability in humans (Non Observed Adverse Effects Level (NOAEL)). Over a lifetime, we ingest about 10 g of Ag in drinking water [49]. Furthermore, Ag can favor the migration of Al in food. The potential exposure for a 60-kg adult can be estimated at a range of 4.4 % Training Within Industry (TWI) 1 mg/kg bw/week [57].

Silver particles/nanostructures have been used as an effective antimicrobial agent in food and beverage storage for a long time. Silver containing plastics had been incorporated in refrigerator liners and food storage containers [58-60]. FDA has been approved the use of silver based particles for disinfection purpose for the food contacting materials [61].

Silver based nanomaterials and nanocomposite can be devised for the easiest detection of commonly found food adulterants, chemical contaminants, allergens and any changes respond to environmental conditions etc. Silver nanoparticles incorporated cellulose pads are used to control the food pathogens from packed beef meat and reduce the microbial count in fresh cut melon [62]. Apart from this, silver nanoparticles slower the ripening times of stored fruits by catalyzing the destruction of ethylene gas and increase the shelf lives of stored fruits [62]. Several studies have demonstrated the efficacy of silver nanoparticles loaded packaging materials in campaigning against microbial growth in foods [62-65]. Nanostructured antimicrobials have a higher surface area-to-volume ratio than their microscale counterpart and their incorporation in food packaging systems are supposed to be particularly efficient in their activities against microbial cells [66]. The development of stable, mono dispersible, metallic silver nanostructures synthesis via reliable green synthesis has been an important aspect of current nanotechnology research. The aggregation of silver nanostructures and the insufficient stability of their dispersions lead to loss of their special nanoscale properties. Researchers employ polymer–assisted fabrication routes and various chemical stabilizing agents (surfactants such as CTAB, SDS etc., and polymers such as PVP) for preventing the selfaggregation of nanostructures [67-69]. The use of chemical compounds is toxic and will reduce the biological applicability. The use of natural products such as biosurfactant, monosaccharides, plant extracts etc. as enhancers and stabilizing agent for silver nanostructures synthesis were extensively studied. The marine glycolipid biosurfactant stabilized silver nanoparticles were synthesized by Brevibacterium casei MSA19 under solid state fermentation using agro-industrial and industrial w aste as substrate [70]. Apte et al. [71] studied L-DOPA mediated synthesis of melanin by fungi Yarrowia lipolytica and the induced melanin has been exploited in the synthesis of silver and gold nanostructures.

As melanin pigments are used as food colorant and nutritional supplements, which reflects the industrial need to large scale production as natural ingredients. Natural pigment production especially from microorganisms is emerging as an important aspect due to their wide acceptance in various industrial sectors [72] and it replaces the chemically synthesized pigments which cause harmful effects in the natural environment [73]. The microbial pigment, melanin has received considerable attention because of their useful biological activities especially in food and pharmaceutical industries. Melanins are high molecular weight pigments that are produced in microorganisms by oxidative polymerization of phenolic or indolic compounds with free radical generating and scavenging activity [74]. Based on chemical structure, properties and species affiliation, melanins are classified as allo-, pheo-, and eumelanins. The black or brown eumelanins are produced by oxidation of tyrosine through tyrosinase to DOPA (o- dihydroxyphenylalanine) and dopachrome, further the cyclization mediates to form 5,6-dihydroxyindole (DHI) or 5,6-dihydroxyindole-2-carboxylic acid (DHICA) [75]. The yellow-red pheomelanins are synthesized like eumelanins in the first step; the intermediate DOPA undergoes cysteinylation, directly or mediated by glutathione to form various derivatives of benzothiazines [76]. The third types of allomelanins are heterogenous group of polymers synthesized via pentaketide pathway [77]. Brown pigments may also produce from L-tyrosine pathway via accumulation and autooxidation of intermediates of tyrosine catabolism [75]). Microbial melanin has a wide range of applications including photoprotective, radioprotective, immunomodulating, antimicrobial and antitumour activities [78-

80]. Actinobacteria were resilient bacteria found among culturable sponge microbes and are current focus on bioactive leads from marine environment [81]. The sponge associated actinomycetes has wide application as antiviral, antibacterial, antitumour, antihelminthic, insecticidal, immuno-modulator, immuno-suppressant and food colorants [82]. Melanin producing microorganisms are ubiquitous in nature; however limited literature is available on actinobacterial melanin production at different cultural conditions.

In the study [Ref-AgNP], rapid reliable approach has been developed to produce uniform silver nanostructures by purified melanin from marine Nocardiopsis alba MSA10. The study [83] aims to enhance the production of melanin from marine actinobacterium N. alba MSA10, by optimizing various cultural and environmental parameters under submerged conditions as well as melanin mediated synthesis of silver nanostructures.

As a potent antimicrobial agent, silver nanostructures have been used in nanosensors and nanomaterial-based assays for the detection of food relevant analytes such as organic molecules, aroma, chemical contaminants, gases and food borne pathogens. In addition silver based nanocomposites act as an antimicrobial for food packaging materials. In this prospective, the food grade melanin pigment extracted from sponge associated actinobacterium Nocardiopsis alba MSA10 and melanin mediated synthesis of silver nanostructures were studied [83]. Based on the findings, antimicrobial nanostructures can be developed against food pathogens for food industrial applications.

4.2.3 Zinc Oxide E6

The ZnO (Chemical Abstracts Service Number (CAS No.) 1314-13-2, Enzyme Commission Number (EC Number) 215-222-5) is a water-insoluble material with ≥ 99.0 % purity. It is a semiconductor which use has increased given that it is a nontoxic biocompatible material showing good optical and mechanical properties [84]. It has been used in the rubber, pharmaceutical, and cosmetic industries; in photocatalysis; and also for therapeutic applications. Furthermore, ZnO is one of the most important trace elements in the organism of mammals and is present in the homeostasis, immune responses, oxidative stress, apoptosis, and aging. ZnO is added to many food products such as cereals and dietary supplements as a source of Zn.

Solubility of ZnO in the stomach environment (pH 2.7) has a value of 98.5 % when the particles are smaller than 1 mm [85]. About 25 studies in vivo and in vitro were found in a search conducted in SCOPUS. These studies report the toxicity of the ZnO NP when used in foods (Table 1).

Table 1: In vivo and in vitro effects caused by exposure to ZnO NP

Reference	Model	Concentration	Conclusions
Mu et al. 2014 [86]	Epithelial cells	5.5 µg ZnO/ml	It is suggested that the dissolution and re-precipitation of uncovered ZnO NP cause cytotoxicity (MTT) and DNA damage
Polak N et al. 2014 [87]	*Caenorhabditis elegans* mutant Sylvester and triple knockout sensitive to metal (mtl-1, mtl-2, pcs-1) to ZnO NPs	0–50 mg ZnO/ml	It was observed that exposure to ZnO NP decreased the growth and development of reproductive capacity, and life expectancy effects were amplified in knockout mice
McCracken et al. 2013[88]	C2BBe1 epithelial cell line, a clone of the Caco-2 cells		With ZnO NP in the same concentration, it was observed that medium toxicity in the Lactate Dehydrogenase (LDH) assay and mitochondrial activity decreased, but not the necrosis or apoptosis
Seok et al.2013 [89]	Sprague-Dawley rats	67.1, 134.2, 268.4, or 536.8 mg ZnO/ kg for 13 weeks	Male and female rats had changes in hematological parameters related to anemia and pancreatitis
Sharma et al. 2012[90]	Mice	300 mg ZnO/kg	The accumulation of ZnO NP induces liver cell damage after oral exposure for 14 consecutive days. ZnO NP also induces oxidative stress, which is indicated with the increment of lipoperoxidation

In conjunction with the instability of the ZnO NP, the degree of solubility allows the oxidation and release of Zn+2 into the medium. It has been observed that the NP showing high solubility in a cell culture, such as ZnO NP exhibited higher toxicity in mammalian cell lines than those having low solubility, such as TiO2 NP [86].

ZnO NP is classified as GRAS by the FDA (21CFR73.1991) and as an E6-safe additive by EFSA. Therefore, these NP are commercially produced and used as packing material and food additive [31]. In a study conducted by EFSA in 2012, it was considered that due to the high solubility of ZnO in the stomach environment, the physical and chemical specifications of ZnO (used in several toxicity studies) are incomplete and do not specify the purity/impurities ratio [91], so it was postulated by this body that the oral use of ZnO is safe.

It is generally known that zinc as an essential trace element extensively exists in all body tissues, including the brain, muscle, bone, skin, and so on. As the main component of various enzyme systems, zinc takes part in body's metabolism and plays crucial roles in proteins and nucleic acid synthesis, hematopoiesis, and neurogenesis [92–95]. Nano-ZnO, with small particle size, makes zinc more easily to be absorbed by the body. Thus, nano-ZnO is commonly used as a food additive. Moreover, ZnO is graded as a "GRAS" (generally recognized as safe) substance by the US Food and Drug Administration (FDA) [96]. With these properties, ZnO NPs have received more attention in biomedical applications. Compared with other metal oxide NPs, ZnO NPs with the comparatively inexpensive and relatively less toxic property exhibit excellent biomedical applications, such as anticancer, drug delivery, antibacterial, and diabetes treatment; anti-inflammation; wound healing; and bioimaging [97-100].

ZnO NPs have become one of the most popular metal oxide nanoparticles in biological applications [101] due to their excellent biocompatibility, economic, and low toxicity. ZnO NPs have emerged a promising potential in biomedicine, especially in the fields of anticancer and antibacterial fields, which are involved with their potent ability to trigger excess reactive oxygen species (ROS) production, release zinc ions, and induce cell apoptosis. In addition, zinc is well known to keep the structural integrity of insulin. So, ZnO NPs also have been effectively developed for antidiabetic treatment. Moreover, ZnO NPs show excellent luminescent properties and have turned them into one of the main candidates for bio imaging.

Sharma et al. explored the effects of ZnO NPs on human liver cancer HepG2 cells and its possible pharmacological mechanism [90]. ZnO NPs-exposed HepG2 cells presented higher cytotoxicity and genotoxicity, which were associated with cell apoptosis mediated by the ROS triggered mitochondrial pathway. The loss of the mitochondrial membrane potential could open outer membrane pores which would result in the release of some related apoptotic proteins including cytochrome c into the cytosol and activate the caspase. Mechanistic studies had proved that the loss of mitochondrial membrane potential-mediated HepG2 cell apoptosis was mainly due to the decrease in mitochondrial membrane potential and Bcl-2/Bax ratios as well as accompanying with the activation of caspase-9. Besides, ZnO NPs could noticeably activate p38 and JNK and induce and attract p53ser15 phosphorylation but was not dependent on JNK and p38 pathways (Figure 4). The results [101] afforded valuable insights into the mechanism of ZnO NPs-induced apoptosis in human liver HepG2 cells.

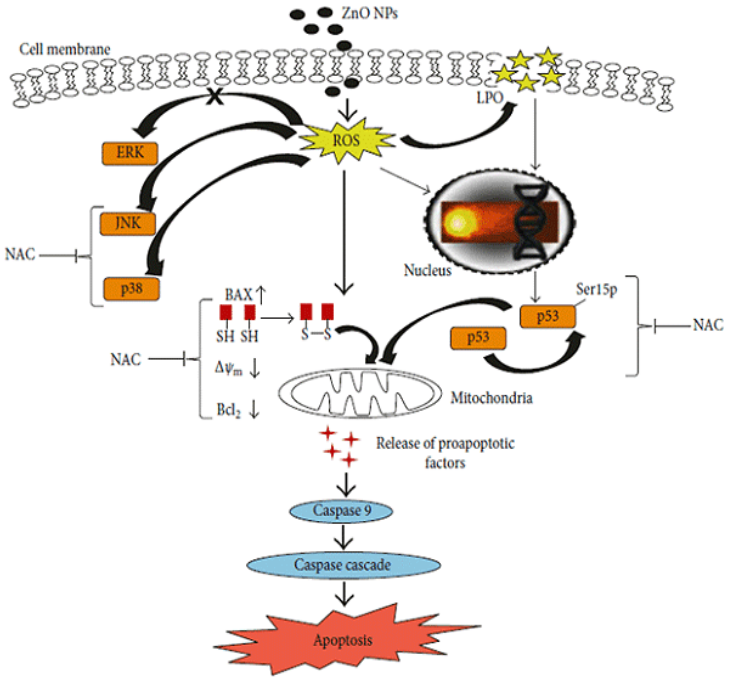

Figure 4: The mechanism of ZnO NPs-induced toxicity in human liver cells [90]. Copyright 2012 Apoptosis

ZnO NPs have exhibited promising biomedical applications based on its anticancer, antibacterial, antidiabetic, antiinflammatory, drug delivery, as well as bioimaging activity. Due to inherent toxicity of ZnO NPs, they possess strong inhibition effects against cancerous cell and bacteria, by inducing intracellular ROS generation and activating apoptotic signaling pathway, which makes ZnO NPs a potential candidate as anticancer and antibacterial agents. In addition, ZnO NPs have also been well known to promote the bioavailability of therapeutic drugs or biomolecules when functioning as drug carriers to achieve enhanced therapy efficiency. Moreover, with the ability to decrease blood glucose and increase in insulin levels, ZnO NPs have shown the promising potential in treating diabetes and attenuating its complications, which can be further evaluated.

ZnO NPs are listed as a kind of safe substance by the FDA. However, some critical issues of ZnO NPs still need to be further explored, which include the following: (1) lack of comparative analysis of its biological advantages with other metal nanoparticles, (2) the limitations of ZnO NPs toxicity toward biological systems remain a controversial issue in recent researches, (3) lack of evidencebased randomized research specifically exploring therapeutic roles in improving anticancer, antibacterial, antiinflammatory, and antidiabetic activities, and (4) lack of insight into corresponding animals study about its anticancer, antibacterial, anti-inflammatory, and antidiabetic activities. Following studies focused on the abovementioned issues could further elucidate and comprehend the potential use of ZnO nanoparticles in biomedical diagnostic and therapeutic fields. We believe that nanomaterials would dramatically promote the development of medicine, and ZnO nanoparticles are expected to make more exciting contributions in these fields.

4.2.4 Silicon dioxide (SiO_2) E551

Silicon dioxide (SiO_2), CAS No. 7631-86-9, is a fine-white powder with a high water absorption rate. It is insoluble in ethanol and water but forms a gel when combined with mineral acids. Particles of this compound are produced on an industrial scale as an additive for cosmetics, medicines, printing toners, and foods. In the biotechnology and biomedical areas, SiO_2 NP has been used as drug development systems, for example, in cancer therapy and in the immobilization of enzymes and DNA transfection [102].

SiO_2 NP are available in the market not as for their use in a specific function. They can have surfaces with positive, negative, or neutral charge and as monodisperse or in the form of aggregates [102]. It has been observed that the industrially attractive physicochemical properties of SiO_2 NP can cause problems in human health [88, 103-105].

There are few studies on the toxicity of SiO_2 for food-related uses. While in the Pubmed database, 945 investigations conducted between 2000 and 2014 with the SiO_2 NP were found, only 10 of them were actually focused on safety aspects when used in food preparations. Some of the studies reviewed showed adverse effects on the GI system [106].

EFSA classified the SiO_2 as E 551. It is a substance recognized as GRAS by the FDA, and its use is permitted in the form of dry powders, salt (and their substitutes), food supplements, rice, and processed cheese. Also, it has been used as a carrier in emulsifiers and colorants at levels reaching a maximum of 5 %. In flavoring, its use at levels of 50 g of SiO_2 NP/kg is allowed (EFSA 2009). Moreover the FDA has authorized the use of the combination of SiO_2 + TiO_2 NP in food to aid solubility of TiO_2 NP (FDA CFR73.575 21).

Synthetic amorphous silica (SAS) meeting the specifications for use as a food additive (E 551) is and has always been produced by the same two production methods [107] : the thermal and the wet processes, resulting in E 551 products consisting of particles typically in the micrometer size range. The constituent particles (aggregates) are typically larger than 100 nm and do not contain discernible primary particles. Particle sizes above 100 nm are necessary for E 551 to fulfill its technical function as spacer between food particles, thus avoiding the caking of food particles. Based on an in-depth review of the available toxicological information and intake data, it is concluded that the SAS products specified for use as food additive E 551 do not cause adverse effects in oral repeateddose studies including doses that exceed current OECD guideline recommendations. In particular, there is no evidence for liver toxicity after oral intake. No adverse effects have been found in oral fertility and developmental toxicity studies, nor are there any indications from in vivo studies for an immunotoxic or neurotoxic effect. SAS is neither mutagenic nor genotoxic *in vivo*. In intact cells, a direct interaction of unlabelled and unmodified SAS with DNA was never found. Differences in the magnitude of biological responses between pyrogenic and precipitated silica described in some *in vitro* studies with murine macrophages at exaggerated exposure levels seem to be related to interactions with cell culture proteins and cell membranes. The *in vivo* studies do not indicate that there is a toxicologically relevant difference between SAS products after oral exposure. It is noted that any silicon dioxide product not meeting established specifications, and/or produced to provide new functionality in food, requires its own specific safety and risk assessment.

The systemic availability of E 551 is very low. There is no evidence for the release of nanosized particles in the stomach, but some dissolution and formation of orthosilicic acid may occur in the lower intestinal tract. None of the tested E 551 products caused any adverse local or systemic effect in oral repeated-dose, fertility, and developmental toxicity studies. In particular, there were no signs indicative of liver toxicity or macrophage-induced liver re-modelling even at very high oral doses. There were also no indications of immunotoxicity or neurotoxicity. Reported effects after low-dose exposure to pyrogenic SAS are all within the

normal physiological range and cannot be considered as adverse. SAS was not mutagenic or genotoxic in vivo. In intact cells, a direct interaction of unlabelled and unmodified SAS with DNA was never found. Differences in the magnitude of biological responses between pyrogenic and precipitated silica described in some *in vitro* studies with murine macrophages at exaggerated exposures seem to be related to interactions with cell culture proteins and cell membranes. The available toxicological evidence in vivo shows that there is no difference in the toxicity of E 551 products, independent of their manufacturing method.

4.2.5 Cobalt (III) oxide (Co_2O_3) E_3

Cobalt oxide (Co_2O_3), CAS number 1308-04-09, is a black powder with molecular weight of 165.8646 g/mol. Its crystal structure is trigonal with a density of 5.18 g/cm3. It is used as a trace element in animal food, and it has been reported to be used as an essential element in the human diet, and its applications likely to increase due to dietary supplements, occupation, and medical services [108].

Co_2O_3 NP accumulates in organisms when consumed and the tissues in which they are mainly found are those of liver, kidneys, bladder, blood, and lungs. This accumulation has been decreasingly observed in a dose–response manner [109]. In addition, the exposure to these NPs is associated with cardiomyopathies and vision and hearing damage when the concentration in cell culture tests is above 700 μg/L (8–40 weeks), whereas at 300 μg/L, hypothyroidism and polycythemia were reported. However, there has been observed that the use of these NP increased the risk of lung cancer induction.

Furthermore, it was observed that the NP of Co_2O_3 can enter the cell cytoplasm in the form of vesicles and can increase the production of ROS [110] and together with TiO2 NP is one of the metal compounds that can yield to photoinduced toxicity [111].

Authorized by the EFSA, the use in animal food and the FDA classifies it as GRAS substance (21 CFR 582.80). However, the exposure limits to Co NP are from 0.02 to 0.5 mg/m^3 (air space), although NIOSH recommends a maximum limit of 0.05 mg/m^3 (airspace) by a working shift.

4.3 Incidental food compounds

4.3.1 Tin Dioxide (SnO2) NP

Tin dioxide (SnO2), CAS number 18282-10-5, is a white powder soluble in water called cassiterite which is the most important chemical source of Sn. It is a colorless solid with a refractive index of 2.006. It crystallizes in the form of rutile, in which the Sn atoms have six coordinates and the oxygen atoms have three [112]. It is an attractive material for its use in gas biosensors [113] and solar cells [114], among others, because of their high transparency and electrical conductivity. SnO_2 NP has been used to develop semiconductor sensors that discriminate samples of virgin olive oil based on its organoleptic characteristics [115].

There are no studies yet regarding the physicochemical properties of the SnO2 NP in the sensors used in food-related systems. There are also no studies analyzing the possible transport of SnO2 NP in sensors to food. Furthermore, when the SnO2 NP are used together with indium in a concentration of 90:10, a compound called indium tin oxide (ITO) is formed. A study showed that chronic and subchronic inhalation of this compound may cause lung toxicity in hamsters treated with 3 and 6 mg/kg of particles of ITO, twice a week for eight weeks [116]. However, the effects of these NP when consumed orally by humans have not been analyzed. No regulations or recommendations by the IARC, NIOSH, FDA, or EFSA were found.

4.3.2 Iron (III) Oxide or Ferric Oxide

Ferric oxide (Fe2O3), CAS number 309-37-1, is an odorless red solid. With insoluble rhomboid structure and 159.69 g/mol molecular mass, it is one of the main iron oxides. The use of Fe_2O_3 NP directly in food had not been reported; there are reports that if for some reason these substances are released into the environment, they are able to modify ecosystems and to reach the products for human consumption such as vegetables and seafoods. The effects of Fe_2O_3< 50 nm NP in two soil types to see the change in the activity of the bacterial community that made it up have been studied [106]. In other works, the effect of Fe_2O_3on watermelon has been evaluated, and it has been proved that these NP can be translocated by plant tissues causing significant physiological changes such as the activity of catalase, peroxidase, and superoxide dismutase; chlorophyll and malondialdehyde content; and the reduction of the ferric reductase activity [117]. In a study with crabs, the Fe2O3 transfer of the muddy sediment in Rhizophora leaves pellet was quantified, finding that the accumulation of metals in mangrove leaves and crabs reflected the chemical composition of the sediments, and that low levels of these compounds were transferred from the leaves and from the crabs to humans [118]. These studies showed that Fe2O3 NP is able to pass through the food chain and reach humans through food. Currently, there are not enough studies on the effects that these NP may have on humans.

Organizations such as the IARC, FDA, and EFSA have not established exposure limits for the intake of these compounds. However, some exposure limits have been reported for the case of NP inhalation: Occupational Safety and Health Administration (OSHA)-The exposure legal limit allowed in the air is 10 mg/m^3, average for an 8-h shift. NIOSH-the exposure legal limit allowed in the air is 5 mg/m^3, average for a 10-h shift. American Conference of Governmental Industrial Hygienists (ACGIH)-The exposure legal limit allowed in the air is 5 mg/m^3, average for an 8-h shift.

Anemia is one of the most prevalent nutritional deficiencies in both developed and developing countries [119]. About 1.62 billion

people or 24.8% of the world population suffer from iron deficiency [120]. According to the World Health Organization statistics, more than half of the anemia in the world is due to iron deficiency [121]. Research in South of Iran reported that 30% of children, 24% of women and 7% of men suffer from anemia. In addition, 13.6% of pregnant women were diagnosed with anemia [122]. Since iron acts as a part of hemoglobin, myoglobin and some of enzymes, iron deficiency can lead to weakness, learning dysfunction, and increase the risk of infectious diseases [123-125]. Furthermore, iron deficiency is associated with increased risk of preterm delivery and low Birth Weight and imposes large costs on the health system [126,127].

Phenylhydrazine and its derivatives are one of the useful compounds in experimental models studying anemia due to their toxic effects on red blood cells (RBCs). Phenylhydrazine leads to RBC hemolysis and induces hemolytic anemia [128]. Hemolytic anemia is a form of anemia which may result from either intravascular or extravascular RBC reduction [129]. Not only iron bioavailability is estimated very low (about 14%–18% for mixed diets and 5%–12% for vegetable diets) but also inhibitors of iron absorption such as phytate, tanenes, and oxalate can worsen this rate [130].

Ferrous sulfate is the common supplement prescribed for anemia shows acceptable absorption, but recent findings revealed that this supplement can cause unfavorable changes in colon bacteria and increase systemic infections and inflammatory signals of epithelium [131-133]. Oral consumption of drugs with low bioavailability needs high dose of the drug to absorb the required amount, but the unabsorbed amount can cause undesirable gastrointestinal complications [134]. When iron is received through the mouth, the lower part of it is absorbed in the upper gastrointestinal tract and the larger part goes through the colon which can react with superoxide and hydrogen peroxide and produce free radicals through Fenton reaction [131]. Therefore, the remaining of free iron can stimulate the intestine, and the created discontent makes the situation difficult for the patient to take the medicine regularly [135].

Ferrous sulfate is the most used supplement for treating anemia, but it can result in unfavorable side effects. Nowadays, nanotechnology is used as a way to increase bioavailability and decrease the side effects of drugs and nutrients. The effects of nanoparticles containing iron on blood and inflammatory markers in comparison to ferrous sulfate in anemic rats has been studied [136]. It was found that single dose of nanoparticles containing iron showed more bioavailability compare to single dose of ferrous sulfate and more efficiently restored hemoglobin, but it was not occurred for the double dose. Furthermore, inflammation measured in both groups received nanoparticles was lower than groups received ferrous sulfate at the end of the experiment.

Conclusions

A report by the British Royal Society notes that we may face a nanotoxicitycrisis in the future. Some of the NP previously classified as safe for human consumption by international organizations are, in fact, more dangerous than previously thought, causing effects such as increased ROS amounts and inflammation in cells. Currently, the development of new NP continues to grow rapidly, given the permitted limits established by these organizations. There are possibilities of developing shapes, sizes, and compositions of many NPs that greatly increase their technological capabilities.

Nanotechnology in one of the novel techniques that recently is using to increase nutrients bioavailability. Researchers showed that when some of the materials are prepared in nanometer size, their bioavailability increases [137-139].With a precise understanding of the properties of nanoparticles such as size, dose, surface chemistry, and structures, we will have useful and safe food products.

Food and related industries such as agriculture, packaging, and food processing have seen huge changes because of the unique properties of nanomaterials. But these unique properties may occasionally lead to ambiguous and sometimes dangerous side-effects to ecosystems and even in people. The main role of nanotoxicology is to provide clear guidelines and roadmaps for reducing risks in the optimal use of nanomaterials. Exposures routes in industrial workers and consumers of food products that contain nanomaterials must be studied carefully.

The use of NP in food is a common practice, since they aid in the preservation and improvement of food quality. There are different exposure pathways for the NP in foods: the exposure can be direct, through regulated additives, or indirectly, through the NP transport from biosensors, packaging, or through the food chain. The NP used to perform toxicological studies is, generally, free of impurities (99%), while in foods, the use of mixes of these NP with others that help improve the characteristics of the product is frequent. The effects that NP will cause to humans will depend on the physicochemical characteristics of the NP aggregates/ agglomerates. NP form stable suspensions as measured by the zeta potential which values range from -20 to - 45 mV. In the monographs by EFSA and FDA it is established that there is a risk when these products are consumed by humans. Some of these NP are only recommended for animal food.

Based on the available evidence, it is concluded that silicon dioxide used as a food additive (E 551) is a substance of very low toxicity which based on the total dietary intake (from its use as a food additive, and its use in dietary supplements) does not represent a human health risk. Any new or novel forms of silicon dioxide that do not comply with established specifications, or are produced to perform a new technological function in food, would require specific safety and risk assessments.

ZnO NPs are listed as a kind of safe substance by the FDA. Due to inherent toxicity of ZnO NPs, they possess strong inhibition effects against cancerous cell and bacteria, by inducing intracellular ROS generation and activating apoptotic signaling pathway, which makes ZnO NPs a potential candidate as anticancer and antibacterial agents. When nanocarriers were used for oral intake of iron, iron

absorption increased 1.35 times compare to the reference ferrous sulfate [140]. In addition, iron absorption from nanoparticles containing iron was 13.42% more than ferrous sulfate in vitro [141]. Therefore, it is expected that with size reduction of iron to nanometer size, its bioavailability increases, and lower doses of the drug would be needed to meet desirable result, which consequently decreases unfavorable effects in gastrointestinal system and encourages the patient to continue the medication.

The melanin pigment produced by N. alba MSA10 can be used for environmentally benign synthesis of silver nanostructures and can be useful for food packaging materials. The characteristics of broad spectrum of activity against food pathogens of silver nanostructures gives an insight for their potential applicability in incorporation of food packaging materials and antimicrobials for stored fruits and foods.

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