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Bioaccumulation and Toxic Profiling of Nanostructured Particles and Materials

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Abstract

Use of nanotechnological based formulations and nanomaterials are increasing day-by-day in wide range covering a broad typology of applications, from design and development of targeted drug delivery systems, manufacturing of pesticides, domestic appliances, textiles, to bioremediation engineering. There are therefore concerns about the environmental risks or bioaccumulation-related issues that may arise particularly resulting from the application of drug-loaded nanocarriers or effect of pesticides that reach the natural ecosystems. This is a major threat in the present era and needs to be balanced against their undoubted benefits to human society. The assessment of the physical and chemical properties of nanoparticles and nanomaterials influencing their toxic manifestation due to accumulation in human or in animal organs is still poorly investigated. This chapter reviews the possibilities of bioaccumulation of different nanoscale particles and materials, their potential acute and subacute toxicological profile and their identification and characterization in different organs and tissues of vertebrates.

Keywords: nanomaterials, nanoparticles, bioaccumulation, characterization, toxicity, analytical methods, in vitro studies, in vivo studies

1. Introduction

Nanostructured materials can be easily accessible to the cellular level of a tissue or an organ in comparison to macro scale particles given their small size that makes them prone to passive entrance. On the other hand the functional performance of nanoparticles depends on their size, morphology and chemical nature of its surface which influence the triggering of phagocytosis through the cellular membranes. Moreover, large pay loads may conduce to stress conditions, and thereby increase inflammation and reduce defense action against pathogens

[1, 2]. It is also known that nanoparticles made up of non-degradable or slowly degradable materials may accumulate at the cellular level hindrance the enzymatic activity of functional proteins [3]. The toxic manifestations may also arise due to their chemical composition and structure, surface charge, solubility and aggregation on the site of elimination or filtration such as at the glomerular filtration of nephrons. In this context, it is fundamental to investigate the aggregation and agglomeration of the nanostructured particles and materials, followed in the ionic environment of the biological fluids to elicit its functional activity and resulting toxicity.

Among available manufactured nanomaterials, titanium dioxide (TiO_2) is one of the most widely used to date [4]. Previous studies suggested that TiO_2 nanoparticles production ranged from 7800 to 38,000 metric tons per year in the USA alone and will be approximately 2.5 million metric tons by 2025 [5, 6]. The fate and bioaccumulation of TiO_2 based nanomaterials (nanotubes TiO_2 -NTs) and nanoparticles (TiO_2 -NPs) in a paddy microcosm over a period of 17 days showed that the Ti levels were the highest in biofilms during the exposure period [7].

Bioaccumulation factors indicated that TiO_2 -NPs and TiO_2 -NTs were largely transferred from low to superior trophic levels [8]. Considering the potential entries of TiO_2 based nanomaterials in organisms, their bioaccumulation throughout the food chain should be regarded with great concern in terms of the overall health of the natural ecosystems [9].

Aquatic floras play a vital role as primary producers of biomass which constitutes the elementary level of food in trophic chains. Environmental exposure of algae to nanoparticles at potential toxic concentrations may affect natural ecosystems by interfering at the basic energy source of the food webs. As an example, Chandler et al. demonstrated that increased alga mortality occurred upon exposure to nano-ZnO and C60 at the size of 1 ppm in comparison to 10 ppm [10].

At the level of primary consumers it was revealed that bioaccumulation of nanomaterials in *Daphnia magna* through alga (used as food source), presented a more toxic profile for zinc oxide in comparison to carbon based nanomaterials which may be explained by its higher solubility [10]. In addition Teer and colleagues investigated the effects of nano-Ag derived from coated AgNPs and AgNO_3 on phosphate availability given its potential as Ag + ligand and as determinant of phytoplankton productivity [11]. It was observed that both nanoparticles accumulated at similar concentrations into the primary producer during high phosphate insult. Yet, AgNO_3 accumulation was only increased for low phosphate condition [11].

Regarding studies at superior trophic level, it was shown that goldfish *Carassius auratus* exposed to 10–100 mg/L of TiO_2 -NPs significantly accumulated these nanoparticles on tissues and organs, namely: intestine from 42.71 to 110.68 ppb and gills from 4.10 to 9.86 ppb. In addition, overall growth inhibition induced by lipid oxidation in the liver was recorded [12]. In other work, Hanna and colleagues investigated the potential ecological damage of an essential trace element - Cu - derived from CuO engineered nanoparticles (ENPs) exposed marine mussels exposed to 3 mg of CuO ENPs for 4 weeks resulting its clearance of ionic Cu which decreased to 48% leading to a reduction in the invertebrates growth rate in comparison

to the control animals, suggesting that CuO ENPs are less toxic than ionic Cu probably due to the slow dissolution rate of the former [13].

Investigation on top predators including humans demonstrated that inhaled nanoscale particles are less cleared by macrophages than large sized particles [14], and are able to translocate to other organs through circulatory or lymphatic drainage which may increase cytokine production and imbalance in redox potential [15] toward oxidation, leading to inflammation or cell death [16]. Nano sized particles and materials were also demonstrated to be taken up by mitochondria and nucleus of the cell [17] causing DNA mutation [18].

To surmount the health risk and potential toxic manifestations or disease associated conditions resulting from nano-devices or nano-structured materials exposure, efficient multifunctional designs are required to make the most of their interesting features while avoid adverse effects.

2. Mechanism of nanoparticle bioaccumulation and toxic action

Metallic elements such as Ni, Cu, Ti and Ag are increasingly considered as nanoparticles components that are being applied to biocides and antimicrobials [19]. Once release to the natural environment their safety profile is of concern. Studies on their toxicological potential were greatly investigated in aquatic species from invertebrates to vertebrates given that these ecosystems compose the ultimate sink of their fate: zooplankton [20, 21], fish [22, 23], algae [24], marine [25] and fresh water crabs [26]. Overall, these works point to three principal factors as potentially responsible for the metallic nanoparticles toxicity, namely: (i) dissolution rate, (ii) cellular uptake and (iii) induced level of oxidative stress and subsequent cellular damage [27].

Nonmetallic carbon-based nanomaterials such as fullerenes and carbon nanotubes, which are under exploration in cancer drug delivery, were reported to be cytotoxic [28]. Obtained data on cell proliferation of human lung cancer cells and human keratinocytes upon exposure to carbon-based nanomaterials revealed decreased cellular viability [29]. Intravenous administration of single-walled carbon nanotubes on mice showed their long term accumulation in the mammalian organs such as liver, lungs and spleen, which was observed using Raman spectroscopy and TEM technique [30]. In addition, decreased levels glutathione (GSH), and increased malondialdehyde (MDA) levels suggested that the toxicity of the carbon nanotubes is due to oxidative stress [31].

Increased levels of reactive oxygen species (ROS) and malondialdehyde (MDA) were further reported after administration of silica nanoparticles (15–46 nm) at a dose of 10–100 µg/mL in human bronchoalveolar carcinoma cells [32].

2.1. Toxicity of nanoparticles due to dissolution

The toxicity of metallic nanoparticles was found to be dependent on the rate of dissolution of the metal ions from its respective nanoparticulate formulations. Bondarenko and colleagues demonstrated that Zn-ions released from ZnO NPs did not exerted significantly different toxic effects in vivo on different aquatic models, neither in vitro on mammalian cells [33].

Differences were only found on its dissolution rate, which were revealed to be non-species dependent [33]. Under aerobic conditions it was also found a positive correlation among the dissolution rate of AgNPs and their toxicological profile upon exposure of bacteria and zooplankton models [34, 35]. In addition, sub-toxic effects of CuO NPs observed in bacteria seem to be associated with dissolved Cu ions liberated from the respective nanoformulation, triggering ROS production and causing cell death [36].

Regarding non-metallic nanoscale particles, biodegradable polymeric nanoparticles made up of poly-(D, L-lactide-co-glycolide) i.e. PLGA and its derivatives it is known that their drug release is based on the dissolution rate of its surface coating polymeric material PLGA [37]. Nevertheless, it was demonstrated in macrophages that the surface coating of these polymeric nanoparticles may be linked to induced toxicity by increasing oxidative stress levels [38].

2.2. Uptake of nanoparticles and their effects on biological membranes

Metallic nano-sized particles as ZnO NPs, with size inferior to 10 nm, were demonstrated to be highly internalized by prokaryotes in vitro causing cellular damage to both Gram negative *Escherichia coli* and Gram positive *Staphylococcus aureus* [39, 40]. This bactericidal potential was also observed for Ag NPs in the size range of 1–10 nm which was shown to be size-dependent [41, 42]. TEM microscopy confirmed bacteria internalization and showed a uniform pattern of distribution [40]. Even at non cytotoxic concentrations cellular uptake occurred [43].

Regarding the mechanisms of internalization, it was proposed that non-specific diffusion and membrane damage, and porins-specific intake are the potential modes through which the NPs could transverse bacterial wall [44]. Cellular uptake depends on multiple intrinsic (e.g. specific and dependent on the types of cell, tissue or organs) and extrinsic (e.g. NPs size and coating) variables [45]. ZnO NPs functionalization was demonstrated to affect bacteria membrane permeability increasing cellular uptake levels [46]. The hydroxyl groups of polyvinylalcohol (PVA) macromolecule existent on the surface of the coated ZnO NPs was found to disrupt the cellular membrane given its alkaline nature [46]. In case of Ag NPs, it has been shown that certain sizes of these metallic nanoparticles attached to Gram-negative *Escherichia coli* wall, resulting in its perforation which lead to the cell death [47], given that their direct contact with bacteria facilitated their dissolution at cell-NP interface and thus, enhanced their antibacterial effects [48].

In this regard, cationic-NPs have been reported as potential nanoparticles to cause pronounced disruption of plasma membrane integrity leading to mitochondrial and lysosomal damage, and production of autophagosomes, more than anionic-NPs [49]. Also, nonphagocytic cells were demonstrated to ingest cationic NPs to higher extent than anionic NPs [50]. Taking into account their surface charge nanoparticles can influence the selectivity and efficacy of drug delivery and imaging by selecting either a phagocytic or non-phagocytic pathway [51].

To evaluate cellular uptake of polymeric nanoparticles composed of poly-(lactic-co-glycolic acid) (PLGA) and coated with PVA and vitamin E TPGS, human colon adenocarcinoma cells were exposed in vitro [52]. It was found that vitamin E TPGS-coated PLGA NPs showed 1.4 folds higher cellular uptake than that of PVA-coated PLGA nanoparticles [53]. Cryo-SEM and

TEM analysis confirmed the cellular internalization, indicating that NPs surface modification with vitamin E TGPS and PLGA enhance loading of chemotherapeutic agents to be administered through oral route for cancer therapy [54].

2.3. Oxidative stress induced via nanoparticle and nanomaterial cellular uptake

Oxidative damage, caused in consequence of cellular internalization of NPs, has been considered one of the main causes of NPs cytotoxicity [55]. ZnO, CuO and Ag NPs, were already reported as ROS levels disruptors in aquatic microorganisms [56].

Also, the toxic effects of ROS generating potential of engineered Ag NPs were tested on different strains of recombinant *Escherichia coli* mutants and that of wild type strain [57]. The results showed that mutant strains of recombinant type were 15 folds more responsive to Ag NPs than the wild type [58]; although, analogous effects were observed for Ag ions [59]. In eukaryotes, induction of ROS by Ag NPs exposure was also observed in zebrafish *Danio rerio* [60].

It is well known that ions of redox-active metals, including Cu, may yield free radicals via the Fenton-type reaction and inflict intracellular oxidative stress [61, 62]. The Cu (II) ions can be transformed to Cu (I) ions in the presence of biological reducing agents such as ascorbic acid or glutathione (GSH), and consequently generate reactive hydroxyl radicals from hydrogen peroxide [63]. Using luminescent bacterial tests in recombinant *Escherichia coli* strains, ROS generating potential of aqueous suspensions of CuO NPs was demonstrated [58]. It has also been shown that CuO NPs induced oxidative stress and DNA damage in these recombinant bacteria strains at low subtoxic concentrations of 0.1 mg Cu/L [58].

In vivo investigation of the exposure effects of ZnO NPs on isolated rat liver mitochondria showed increased mitochondrial membrane permeability prone to energy dissipation [64], ROS levels production caused impairment of the mitochondrial respiratory chain and even apoptosis [65]. Similarly, the experiments on isolated human liver cells in-vitro showed ROS triggered mitochondrial pathway resulting apoptosis and cell death [65].

Moreover, it was also demonstrated a concentration dependent genotoxicity derived from exposure of several nanoparticles composed of α -alumina, β -alumina, SiO_2 , SbO_3 , and Fe_2O_3 through generation of excess ROS, which led to DNA strand breakage [66]. DNA cleavage, an indicator of irreversible completion of apoptosis, occurred in organisms exposed to 500 $\mu\text{g}/\text{kg}$ of the above-mentioned precipitated nanoparticles [67]. Moreover, cleavage of inter-nucleosomal DNA ladder bands occurred upon exposure to 500 $\mu\text{g}/\text{kg}$ of γ -alumina and α -alumina [66].

3. Conclusion

Nano-scale particles and materials applications are increasing significantly and thus their potential environmental and human health risks urges consideration. Analytical methods are required to reliably detect and characterize nanoparticles and nanomaterials in the natural environments, and their properties once interacting with complex matrices such as air,

soil and water, as well as food and consumer products. Advances in engineering particles and materials testing, either qualitative or quantitative determinations, should be pursued to ensure a safety profile, including the development of standard guidelines. In addition to the toxicological studies, various uptake paths have to be investigated, including dermal, oral and intestinal routes, as well as bioaccumulation trials and potential long-term effects consideration. Research into new analytical methods is further required to address the special properties for the establishment of ecological and human health risk factors.

Disclosure statement

No conflicts of interest.

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