Toxicity of nanoparticles: A development opportunity in environment and health.

José Roberto Vega-Baudrit*, María Camacho-Murillo, María Obando-Víquez, Sandí-Montero Lilia

Department of Forensic Toxicology, School of Chemistry, National University. Costa Rica, Heredia

Abstract

Nanoparticles have a promising future for application in various fields. They provide a development opportunity for scientists and workers from different areas of being able to work with materials at the nano-scale, because their development influences many jobs that include treatments against diseases, biological controls, ethical development, and environmental control. However, it is a field that is rapidly advancing in terms of its industrial production, but not so much in the study of possible adverse effects, so there is a large information gap, which paints an uncertain picture. There are several routes of exposure, among the most relevant, are the inhalation, dermal and ingestion, where the inhalation is the most recurrent and there are already registered cases of different lung pathologies and even the presence of cancer. Regarding the environment, there are plenty of routes and methods for nanomaterials to enter into aquatic and terrestrial ecosystems. Even though there are assessments related to the effect of some nanoparticles on some species, the results should not be generalized as each material reacts differently, which leaves us with much more research needed. In the ethics area, many studies indicate that the potential for contamination should be reduced and that is why it has been considered during the development of nanoproducts, their production and manufacturing, as well as their possible implications for health.

Keywords: Nanotoxicology, Health, Environment, Nanoparticles, Nanotechnology, Toxicity.

Introduction

Advanced technology gives us the opportunity of studying from macro to nanoparticles. Nowadays we have this opportunity that is nanotechnology. Nanotechnology is the study of extremely small structures; also, it is the treatment of individual atoms, molecules, or compounds into structures to produce materials and devices with special properties. Nanotechnology involves changing individual atoms and molecules into nanostructures and more closely resembles chemistry biology [1].

It is also inherent to these materials to display different properties such as electrical conductance chemical reactivity, magnetism, optical effects, and physical strength, from bulk materials as a result of their small size [1]. Nanotechnology refers to technology at the nanoscale that has applications in the real world; it is a broad and highly interdisciplinary field that is still evolving [2].

Nanotechnology works on matter at dimensions in the nanometer scale length, and thus can be used for a broad range of applications and the creation of various types of nanomaterials and nanodevices so; nanomaterials are commonly defined as those materials with very small components and/or structural features with at least one dimension in the range of 1-100 nm [3].

Everything involving nanomaterials is of relevance because these materials have enabled promising new opportunities in oncology for treatment of cancer with nanomaterial- based drug delivery strategies, in which anti-cancer drugs are loaded directly into nanomaterials and transported to the specific tumor tissues for cancer-killing [4]. The opportunity of curing cancer with these technologies nowadays has become very important in a decade for biomedical studies; however, it has also become a problem when searching for the toxicity of these nanomaterials. That is why toxicity needs to be evaluated in model systems, which are relevant and predictive of human physiology, yet convenient, affordable, fast, and ethical to allow for thorough and systematic evaluation at a high scale [5].

Therefore, many studies have evaluated the toxicity of different materials from zebrafish to biomedical. Scientists are now utilizing this principle to fabricate complicated, yet highly ordered, microstructures at the nanometer- length scale and if they work with these nanomaterials, different parameters can be assessed, such as hatching, organ development, (swimming) behavior, immunotoxicity, and genotoxicity, in addition to reproductive toxicity and mortality [6].

***Correspondence to:** José Roberto Vega-Baudrit, Department of Forensic Toxicology, School of Chemistry, National University. Costa Rica, Heredia, E-mail: jvegab@gmail.com

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Nanotoxicity

Nanotoxicity is the study of the toxicology in nanoparticles (NPs), for a better understanding and assessing the health risks involved in the use of NPs [7]. Being more specific, the particle size and surface area are considered important factors that contribute directly and significantly to the toxicity of NPs, with smaller sized NPs exhibiting higher toxic effects due to increased surface area [8] (Figure 1). For a better understanding, despite the extensive use of nanomaterial today, there is still a limited understanding of nanomaterial-mediated toxicity *in vivo*, and scientists have thought the Drosophila model presents an interesting alternative in the study of nanotoxicity [9]. Now the studies about nanotoxicity involved also non-mammalian *in vivo* models and they have also enabled a greater understanding of the toxicity effects [9]. Some examples are Caenorhabditis elegans (roundworm) and Danio rerio (zebrafish) [5]. Besides, *in vitro* alternatives would allow for faster testing, and using a range of cellular models is proposed as a beneficial strategy to nanotoxicology [10,11]. In addition, cultured human and animal cells can be better controlled and therefore yield more reproducible data than *in vivo* systems; however, they require a high standardization to maximize reproducibility [10].

On the other hand, Georgina Harris in "*In Vitro* Resilience and Nanotoxicity In 3D Brain Models", uses a 3D *in vitro* dopaminergic model to study acute, delayed and repeated- dose effects, neuronal resilience and 3D models for nanotoxicity testing neural cells. In her discussion, she says that the potential of the 3D models to induce nanotoxicity needs to be considered, so it might be important to consider what she says because if we try to make some organs with cultured *in vitro* nanomaterials, it could be problematic if they do not consider the possibility of nanotoxicity in a 3D printer and it could be a problem for future transplants and human health.

Now, if we only consider human health we are wrong because there is also a basis for concern regarding environmental impacts and areas such as ecotoxicology, environmental chemistry, behavior, and fate are areas of concentrated current research [12,13]. Table 1 illustrates some list of the toxicity of engineered metal NPs.

One of the most common routes of exposure is by inhalation. These particles because of their aerodynamic capacity can be deposited in the nose, throat, and travel to the pulmonary epithelia More than 50% of the particles between 15-20 nm can be deposited at the level of alveoli. A clear example is studies of TiO2 NPs that migrate from the pulmonary epithelial surface and can reach extra pulmonary organs. On the other hand, the scope that NPs can reach by the circulation in our body is not yet well known, as well as the defense mechanisms and because of which we discard them.

Dermal route

There is missing information and specific experimental studies in this area. It was previously believed that the skin did represent a barrier to these particles; however, recent studies showed that these are capable of penetrating the skin, according to the size of the nanoparticle and its composition. On the other hand, experimental studies in which TiO_2 particles are injected subcutaneously end up being deposited in lymphoid nodules, liver, and spleen.

Via ingestion route

This is one of the most promising pathways for digested manufactured NPs, as drug vectors, in the pharmaceutical industry and there are no studies that indicate factors of importance for their bio toxicity, so it is still an unknown issue.

There are very few publications of scientific articles, where they have carried out experimental research on the metabolism or pathways of biological degradation of NPs. A presentation of a route outside the most common and previously analyzed is a study in rats where it was found that carbon nanotubes were excreted in the urine after being injected intravenously. Radiolabeled carbon nanotubes were the technique to give them segmentation.

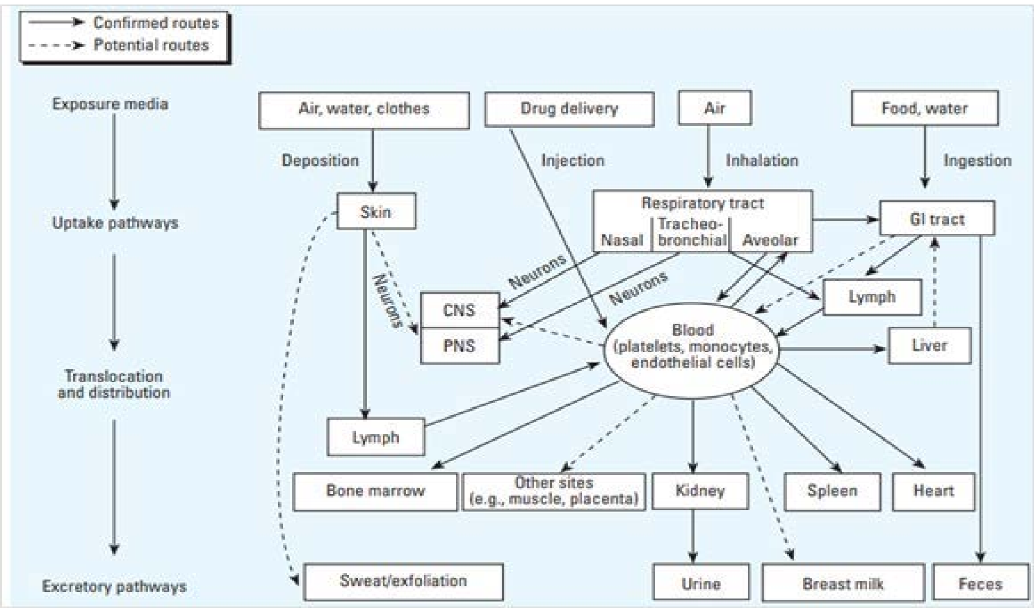

Figure 1. *Principles for characterizing the potential human health effects from exposure to nanomaterials.*

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Table 1. *List of some existing toxicity of engineered metal nanoparticles and their health and environmental effects [12].*

Nanoparticle	Environmental effects	Health effects
		Aptosis, decreased cell viability, lung toxicity,
Carbon nanotubes	Cause indirect effects upon contact with the surface of the environmental	oxidative stress, retarded cell growth, skin
	organism, environmental damage	irritation, etc.
	Effects on soil organisms and enzymes, aquatic ecosystems, binding of chemicals to fullerenes may affect the toxicity of other environmental	
Fullerenes	contaminants	Retarded cell growth, decreased cell viability, oxidative stress and aptosis, etc.
		Arrest of cell growth and sometimes even cell death, chromatin condensation, free radical
Heterogeneous nanostructures	Toxicity depends on multiple physicochemical as well as environmental	formation.
	factors, adverse influence of ecosystem, etc.	
		Alterations of the non-specific immune responses,
Nanosilver	Undergoes several transformations when it is released into the environment	altered cell signaling, apoptosis, necrosis of cells, oxidative stress, etc.
	and shows adverse effects	
Nanostructured	List	List
	Persistent and tend to accumulate in the environment, toxic to plants, wildlife,	Oxidative stress, fibrosis, cardiovascular effects,
flame retardant	etc.	cytotoxicity, carcinogenic, etc.
Polymeric		Oxidative stress, inflammation, alteration in
nanoparticles	Potential hazardous factor for environmental exposure.	cellular morphology and functioning, etc.
Silicon based	Potential hazardous factor for environmental exposure, adverse influence of	Cardiovascular effects, cytotoxicity, increase
nanoparticles	ecosystem, etc.	oxidative stress, etc.
TiO2	List	List
		Excessive exposure in human may result in increased oxidative stress, retarded cell growth,
Nanoparticles	Disrupt and aquatic ecosystem's carbon and nitrogen cycles, stress photosynthetic organism.	slight changes in lungs, etc.

Associated diseases

Currently, there is literature regarding experiments both *in vitro* and in animals that show that certain types of NPs could present risks such as inflammatory and potentially toxic biological activity, including tumorigenicity [2,5,6]. It has ventured into the conduct of toxicity tests to try to associate them and see if they are involved in different pathologies. Those suggested to be performed at the entrance of lungs, skin and mucous membranes, and verified toxicity in key organs, as well as endothelium, blood, spleen, liver, nervous system, heart, and kidney. On the other hand, more precise analysis and research are required, such as the evaluation of the durability of the NPs, their interactions, and the activity within cells (Figure 2) [7].

Studies have been conducted to research the toxicity of NPs focused on the atmospheric exposure of humans and environmentally relevant species of environmentally produced ultrafine particles, coming from combustion processes (automobiles) and other sources of contamination. Pulmonary toxicity studies were conducted of each organism, associated with the deposition of these NPs in the respiratory tract, finding evidence of a high risk of asthma in children and adults. However, other research does not indicate the same correlation [8]. At the level of the respiratory tract, effects have been reported on the lung parenchyma and associations have been established between exposure to carbon nanotubes, and cases of rapid progressive interstitial fibrosis, in experiments performed on mice after exposure by inhalation. Carcinogenicity effects and tumor formation as granulomas were also found [3,8]. Another NP that has shown adverse effects in animals is TiO_2, which in turn the IARC determines as a possible carcinogen for humans [9]. Among the huge variety of complex nanomaterials, the TiO_2 NP titanium dioxide NPs are characterized by being one of the most globally produced nanocomposites, also representing great economic value. They are currently among the components of numerous foods, cosmetics, paints, and hygiene items available in the market. Although there is evidence that their size and nanometric properties favor the accumulation in the liver and other tissues, the information obtained about their genotoxicity has not been conclusive to date [3].

Another case was presented of a person who had occupational exposure to dendrimers in a research laboratory, which caused Erythema multiforme. It was attributed to the above because it reappeared when he returned to the job, consisting of a response to allergic contact dermatitis.

In tests with humans, using inhaled radiolabeled carbon NPs, it was learned that these particles are translocated to the systemic circulation. However, another similar study found no significant translocation of NPs to the general circulation. So, although it has been shown in some studies that NPs can pass into the circulatory system, it has not yet been determined what biological effects can be derived from this systemic transport.

Nanoparticles in the environment

As new uses and applications of engineered nanomaterials (ENMs) have increased enormously in the last decades, so have done the concerns about their environmental implications, yet the majority of these implications remain unknown or still

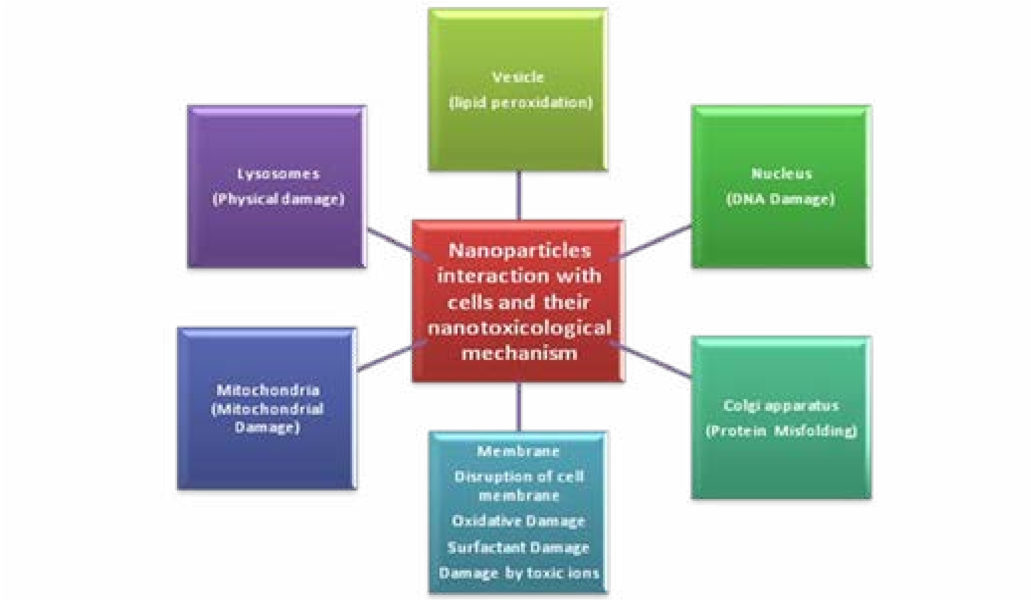

Figure 2. *Nanoparticles interaction with cell & their nanotoxicity mechanism.*

not fully understood. Just as the importance of knowing and determining their potential toxicity, there is a need to estimate the concentration of specific ENMs in different environmental media as well as the response that environmental receptors may have. Since NPs don't display the same reactivity or interactions as the bulk material, it becomes pretty important to study each type of NP, focusing on the possible risks without generalizing the obtained results to every kind of NP, because of the unique properties and how they may influence toxicity. In addition to all the patches we still find regarding the reactivity and interaction of NPs themselves with the environment, leaving alone the toxicological effects they could have when they come accompanied with other residues in waters, most of the tests done so far do not include multicomponent systems and they are not suited for chronic effect quantification.

Due to the increasing applications of NPs and the multiple ways developed for their use, their pathways for entering the environment have diversified too. Coatings, paints and pigments, catalytic additives, and cosmetics are the best examples of products containing NPs. As entering the environment along their life cycle, there are three emission scenarios mentioned generally: (i) release during the production of raw material and nano-enabled products; (ii) release during use; and (iii) release after disposal of NP containing products (waste handling). The emissions can be directly to the environment or indirectly via a technical system like a wastewater treatment plant or landfills.

NPs may enter aquatic systems directly through industrial discharges, by disposal of wastewater treatment effluents, and indirectly through surface runoff from soils. Multiple authors have reported different effects that NPs can have on aquatic species, for example, a study practiced in Daphnia magna, showed that NPs of TiO_2 (~100 nm) were more toxic than the non-nanosized particles of TiO_2 (~200 nm) and an exposure of 96 h to a concentration of 2 mg/L nanosized TiO_2 created a coat over the exposed organisms that reduced the molting rate to 10%, leading to a mortality of 90% [9].

According to some references, silver NPs (AgNPs) are the most widely used metal NPs due to their antibacterial properties. The estimated annual production exceeds 1000 tons/year. AgNPs can enter the environment as aggregates and soluble ions, which can be toxic to aquatic organisms. It is estimated that more than 15% of Ag released into waters come from materials or residues containing AgNPs. These NPs are known to induce the production of reactive oxygen species (ROS) and as a way to cope with the stress, aquatic microorganisms modulate their physiological and biochemical metabolism through antioxidant defenses like antioxidant enzymes. These demonstrated that AgNPs are capable of causing acute toxicity in Potamonautes perlatus, a freshwater crab; however, the toxicity differed significantly according to AgNP concentration and exposure temperature. They tried different treatments depending on concentration and temperature, observing mortalities only in the 1000 µg/mL and 10,000 µg/mL treatments, compared to other treatments with concentrations between 0µg/mL and 100µg/mL. Then, the temperature treatments showed mortalities at 28°C, but not at 18°C or 22°C. The mortality data during the experimental periods indicate that the AgNPs and temperature combinations were toxic to the survival of *P. perlatus.*

Regarding terrestrial environments in current times, particulate matter at the nanoscale is progressively released from devices, goods, personal care items, and agriculture- intended products. Recent reports indicate that industrial facilities, cars, trucks, agriculture and farming equipment, agricultural applications of nanotechnology, and the constant increase of nanomaterial's in biosolids have dramatically increased the risks of plant exposure to particulate matter.

In 2013, Qian et al. compared the toxic effects of AgNPs and Ag^{+} on Arabidopsis thaliana at the physiological, ultrastructural, and molecular levels [4]. They found that AgNPs did not

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affect seed germination; however, they showed a stronger inhibitory effect on root elongation than Ag^+. Also, they found that AgNPs could be accumulated in leaves, which absorbed AgNPs, disrupted the thylakoid membrane structure, and decreased chlorophyll content, which can inhibit plant growth. Compared with Ag^+, AgNPs could alter the transcription of antioxidant and aquaporin genes, indicating that AgNPs changed the balance between the oxidant and antioxidant systems, and also affected the homeostasis of water and other small molecules within the plant body. In the end, this study suggests that AgNPs could be more toxic than Ag^+.

Lin and Xing in 2007 made a study on the effects of five types of NPs (multi-walled carbon nanotube, aluminum, alumina, zinc, and zinc oxide) on seed germination and root growth of six higher plant species: radish, rapeseed, ryegrass, lettuce, corn, and cucumber [5]. They found that seed germination was not affected except for the inhibition of nanoscale zinc (Zn NPs) on ryegrass and zinc oxide (ZnO NPs) on corn at 2000 mg/L. This concentration also terminated root elongation of the tested plant species. Fifty percent inhibitory concentrations (IC50) of Zn NPs and ZnO NPs were estimated to be near 50 mg/L for radish, and about 20 mg/L for rapeseed and ryegrass. These results become significant in terms of the use and disposal of ZnO NPs, which are being used in personal care products, coating and paints, on account of their UV absorption and transparency to visible light.

In the case of terrestrial invertebrates, Khare did a study on the adverse effects of TiO_2 and ZnO NPs in a soil nematode, Caenorhabditis elegans, using different sizes of NP, <25 nm and <100 nm, finding that the smaller NPs showed LC50 of 77mg/L for TiO_2 and 0.32mg/L for ZnO, while the bigger ones of TiO_2 were non-toxic, and the ones of ZnO showed LC50 of 2 mg/L. They concluded that the smaller NPs in both cases were more toxic. Using the same compounds, another study by Hu was conducted on earthworm Eisenia fetida to evaluate their toxicities in soil. To accomplish this, artificial soil systems containing distilled water, 0.1, 0.5, 1.0 or 5.0 g/kg of NPs were prepared and earthworms were exposed for 7 days. Contents of Zn and Ti in the earthworm, the activities of antioxidant enzymes, the DNA damage, the activity of cellulase, and damage to mitochondria of gut by workers; implementation of controls; choice of participation in medical screening; and adequate investment in toxicologic and exposure control research.

The last diagram clearly indicates that some basic research studies are needed to understand the behavior of nanomaterial's in the human body and the environment, in order to minimize the nanoethics issues for the public. As shown, all the elements provide a safer nanotechnology practice for producers, users, and the environment.

Furthermore, one of the problems is that this new nanotechnology has to need to be normalized in terminology; therefore, different European institutes dedicate to normalize more in their national ambit than internationally. They have been worked together and created different committees about normalization, like ISO TC229 "nanotechnologies", CEN TC 352 "nanotechnologies", IEC/TC 113, OECD Working Group of manufactured nanomaterials, REACH: Regulation (CE) 1907/2006 Concerning the registration, evaluation, authorization, and restriction of chemical substances and preparations and The European Commission. For REACH it's not specific but nanomaterials come under the definition of "substance", although they should be included as a highly concerning substance and their health effects and environmental effects properly evaluated, before their use and commercialization, because their effects are unknown [6].

Scientists, like toxicologists, have the important work to identify key factors or tests that can be used to predict toxicity, permit targeted screening and allow materials scientists to generate new, safer NPs with this structure- toxicity information in mind.

It is still necessary to do a lot of research in the environmental area, since most of the particles behave differently, causing then the existence of many forms of toxicity. As it is evident throughout the review, the particles of TiO_2 and ZnO are within the most investigated. This is due to the great production and use they are subjected to. As mentioned, they can be harmful to some species, and measures will be needed to avoid an excess of these that seriously affect the environment.

Conclusion

Nano ethics has to have more studies on the proper treatment of nanomaterials and nanotechnology. For the safety of scientists and workers, there should be a control in measuring products. Nobody should have an advantage with the wrong production, which in this case can have an impact on the environment and human health.

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