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ARTICLE

Nanosilver: Properties, Applications and Impacts on Health and Environment

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ABSTRACT

Nanotechnology has developed rapidly in the last decade as a multidisciplinary field, with a myriad of applications in strategic areas including energy, electronics, medicine, biotechnology, among others. In modern days, the high commercial demand of silver nanoparticles (NPAg), in particular, has motivated a broad debate in the scientific community. This review gives a brief survey of the applications, commercialization and possible impacts of NPAg to human health and environment, with focus on their toxicity, transformation, and bioavailability. We also present a description of the current international laws and regulations regarding commercialization of nanomaterials.

KEYWORDS: Nanosilver; Silver Nanoparticles; Nanomedicine; Nanotoxicology

Introduction

Nanoparticles (NPs) have extremely small dimensions, on the order of tens of nanometers; they have a large surface area and exhibit mechanical, optical, magnetic, and chemical properties that are different from other particles and macroscopic surfaces. The use of these properties in technological applications is the basis of nanotechnology[1]. However, the properties that make nanomaterials so attractive, such as small size, varied shape, and high surface area, may also be responsible for environmental contamination and harmful effects to humans and other living organisms[2,3,4,5].

The progress of nanotechnology is boosting the global market and increasing the consumption of materials, products, and processes related to this area. This trend is corroborated by the application of nanomaterials in various segments, including food, electronics, pharmaceuticals, biotechnology, cosmetics, healthcare, and agriculture[6,7]. Consequently, various NPs are being synthesized, processed, and discarded in increasingly larger quantities, without prior knowledge of the possible toxic effects[8]. Among these NPs, the predominant ones are metallic NPs, including silver (Ag NP) and gold (Au NP); oxide NPs, primarily from iron and titanium oxide; and polymer, semiconductor, and carbon-based NPs[9]. The extensive development and application of NPs has raised concerns about potential health and environmental risks[1]. Despite great efforts for studying the interaction of NPs with biological systems, little is known about their bioavailability, biodegradability, and toxicity in different systems.

Among the metal NPs currently under study, Ag NPs, also known as nanosilver, represent one of the major systems for health applications because of their biocidal characteristics, low cost, and ease of preparation. However, some of these beneficial features may also pose hazards to humans[10,11] and other living organisms[12,13,14,15,16,17], resulting in a negative impact on both the environment and public health.

Although the toxicity of silver is well characterized, there is no evidence that Ag NPs from commercial products can affect human health. However, the commercialization of these products may help carry Ag NPs and silver ions (Ag^+) to the environment and ultimately lead to environmental persistence and bioaccumulation[18,19]. Thus, understanding the potential risks of Ag NPs to humans and the ecosystem is crucial, particularly with regard to aquatic environments because of the aggravating global problems related to water availability and the importance of water with regard to public health.

Ag NPs

Among the various types of nanomaterials with potential application in the medical field, we can cite carrier NPs, including liposomes, solid lipid NPs, and nanoemulsions[20]. NPs can also be combined with organic compounds such as chemotherapeutic agents (with cancer-fighting properties) and with inorganic NPs such as metallic particles, oxides (e.g., zinc and iron oxide), and Ag NPs.

Among the various methods available to synthesize Ag NPs, the chemical reduction of silver with sodium borohydride and polyvinylpyrrolidone (PVP), which is used as a stabilizer to prevent aggregation, has been the most common[21]. NPs can also be stabilized through conjugation with different coatings, e.g., Ag NPs conjugated with proteins[22]. In addition, pH, ionic strength, and electrical charge can influence the stability of NPs and thereby influence their size and toxicity mechanisms[23] because NPs of different sizes exhibit different toxicities[24]. In fact, smaller NPs have higher surface areas and may therefore release more Ag^+, thereby exhibiting higher toxicity and higher microbicidal activity[23, 24].

Owing to the lack of international standards on the toxicity of NPs according to size, the toxicological data reported in the literature remain controversial and may vary depending on the cell type under investigation (*in vitro* tests), coating type, and NP size.

Applicable and commercialized Ag NP-based products

Recently, the number of commercialized products containing nanomaterials has considerably increased, and Ag NPs are the most marketed[25]. Due to their physicochemical properties and optical–electronic characteristics, inorganic nanomaterials have great potential as therapeutic molecules against cancer[26]. Ag NPs are thought to be most popular because of their wide applications in biotechnology and medicine, broad spectrum of bactericidal and fungicidal activities[27,28,29], application in the coating of catheters and dressings, and others[30,31]. Recent data have shown that 70% of Ag NPs are used in healthcare and cosmetics and the remaining 30% are used in textiles, food and beverages, electronics, household products, and packaging materials[32].

Toxicity of Ag NPs to human health

Several studies have reported that the cytotoxic and genotoxic potential of Ag NPs is associated with DNA damage, apoptosis, and necrosis and that their main mechanism of action appears to be associated with increased levels of reactive oxygen species (ROS)[11,33,34,35]. As already mentioned, the mechanism of toxicity of Ag NPs remains poorly understood but appears to be related to the particle size and physicochemical characteristics because smaller NPs have a greater potential to invade cells and reach organs such as the lungs in the case of inhalation exposure[36].

The toxicity of nanostructured materials, particularly Ag NPs, has raised concerns about their toxicity to primary organs through the systemic circulation and to other systems, including the cardiovascular and central nervous system (CNS)[37]. A recent study has indicated that Ag NPs can traverse the blood–brain barrier, reach the CNS, and trigger the production of excess ROS[38]. Figure 1 shows the morphological

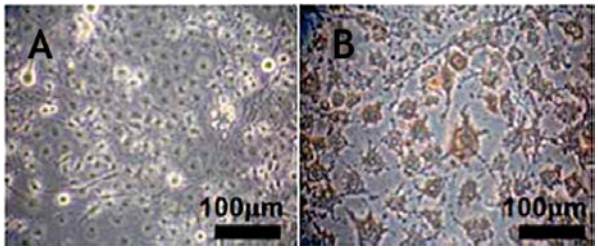

Figure 1. Optical microscopy showing the morphology of U-251 cells not treated with Ag nanoparticles (A) and treated with 200 mgML^{-1} Ag nanoparticles (B). Adapted from Asharani[11].

alterations in human brain tumor cells (U251 cell line) after incubation with Ag NPs.

Inhalation is the preferred route of exposure in the respiratory tract. In the lungs, NPs can target not only epithelial cells but also immune cells such as macrophages and fibroblasts, which play a pivotal role in inflammation, fibrosis, and genotoxicity induced by nanomaterials[36,39].

Cosmetics and personal hygiene products containing NPs also represent an exposure route to the skin, through which these particles can reach the systemic circulation and target organs, including the liver, kidneys, and heart. The liver is responsible for the metabolism and subsequent detoxification of xenobiotics and plays a major role in the defense against harmful agents. Nanomaterials can induce liver injury through distinct mechanisms, e.g., the activation of cytochrome P450[36,39]. Moreover, Ag NPs accumulated in the liver and spleen can reach the systemic circulation[40] and cause imbalance of immune factors, including changes in the cytokine profile, activation of the complement system, and other relevant effects *in vivo*[36,39].

The excessive generation of ROS appears to be essential for the toxic effect of Ag NPs because it causes an imbalance in the cellular metabolism through inflammation; damage to proteins, membranes, and DNA; and impairment of mitochondrial function[41,42 43]. The internalization process is shown in Figure 2.

With regard to DNA damage, although some *in vitro* tests have been standardized by international health agencies, genotoxicity results using various NPs are often controversial, considering that NP size is critical for biological toxicity[41,44]. In this respect, studies using coated Ag NPs have reported no genotoxic effects on different cellular types using particle concentrations > 10 µgML^{-1} and particles with diameter between 6 and 80 nm[10,35,45]. On the other hand, other studies have reported the genotoxic potential of Ag NPs for human cells using particle sizes ranging from 1.5 nm to 70 nm[11,46,47].

Previous studies on the cytotoxicity and genotoxicity of Ag NPs have indicated that NPs induced apoptosis in human blood leukocytes and inhibited the expression of cytokines, interferon, and tumor necrosis factor alpha[46,47]. Other *in vitro* cytotoxicity studies revealed that macrophages of the cell line RAW 264.7 induced apoptosis after incubation with 30 µgML^{-1} Ag NPs for 24 h[48]. In addition, exposure of the THP-1 (human acute monocytic leukemia) cell line to AG NPs at 5 µgML^{-1} for 6 h promoted a significant increase in ROS associated with DNA break in addition to a strong induction of necrosis and apoptosis[49].

Tables 1 and 2 show the main toxic effects of increased exposure to Ag NP in *in vitro* and *in vivo* tests, respectively.

Disposal of Ag NPs in the environment

At present, industrialized nanomaterials can be considered the main source of input of NPs in the environment[60], potentially increasing their availability to biological systems and consequently causing toxicity and environmental contamination. NPs can impact the environment by several routes, including the direct toxic effects on biota, changes in the bioavailability of toxic agents and nutrients, and indirect effects through interactions with natural organic compounds[1].

NPs can be released into the environment by natural or anthropogenic sources[61]. Many geological and biological pro-

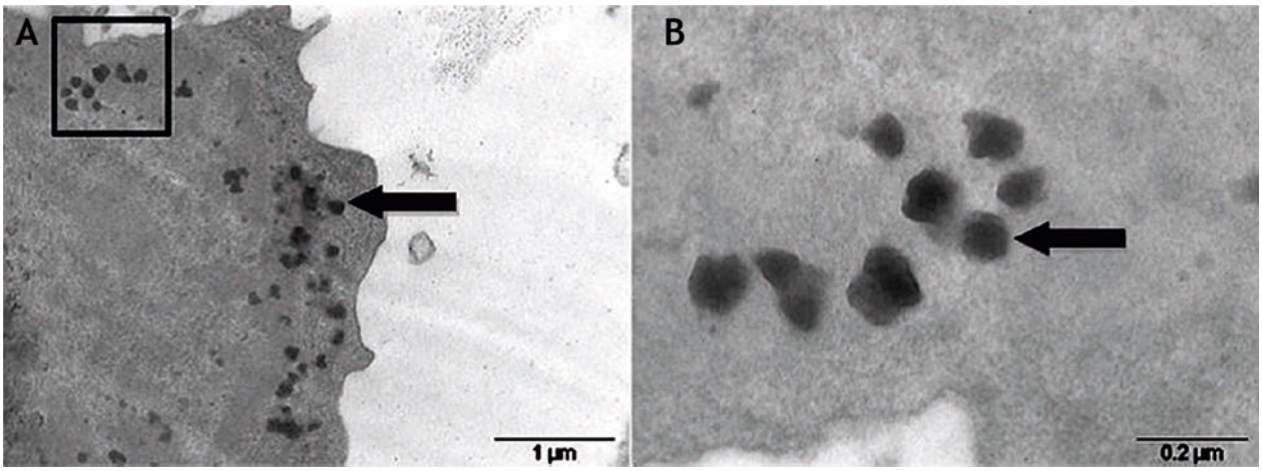

Figure 2. Internalization of Ag nanoparticles into mouse macrophage cells (RAW 264.9 cell line) after 3 h of incubation. A) The internalization was visualized by transmission electron microscopy; B) Enlarged image of Ag nanoparticles. Adapted from Singh48[48].

Table 1. In vitro toxicity of Ag nanoparticles in mammalian cells.

Cell Type	Size of the nanoparticles (nm)	Concentration	In vitro toxicity	Reference
IMR-90 (human lung fibroblast cells) and U251 (human glioblastoma cells)	6–20	50 a 400 μgML^{-1}	Induces oxidative stress and formation of DNA adducts	11
A549 (human lung adenocarcinoma cells)	30-50	> 15 μgML^{-1}	Induces apoptosis and oxidative stress	35
THP-1 (human monocytic leukemia cells)	69	> 7,5 μgML^{-1}	Induces genotoxicity (assessed by the comet assay)	49
Mesenchymal stem cells	46	> 10 μgML^{-1}	Induces cytotoxicity [assessed by the release of lactate dehydrogenase (LD)]	50
Caco-2 (human colon carcinoma cells) and C3A (human hepatoma cells)	35	>1 μgML^{-1} (DL^{50} = 50 μgML^{-1})	Induces apoptosis and increased oxidative stress	51
HepG2 (human hepatocellular carcinoma cells)	7-20	> 250,0 μgML^{-1}	Induces apoptosis and increased oxidative stress	52
HeLa (human cervical carcinoma cells)	2-5	> 120,0 μgML^{-1}	Induces apoptosis, DNA damage (assessed by the comet assay), and increased oxidative stress with increased lipid peroxidation	53
Hepatic cells derived from non-malignant tissues	5-10	4,0 μgML^{-1}	Induces apoptosis and cell cycle arrest in phase G2/M	54
L929 (murine fibroblast cells)	50-100	25, 50 and 100,0 μgML^{-1}	Induces apoptosis increased DNA fragmentation, and mitochondrial and membrane depolarization	55
HT 29 (human colon cancer cells)	172,6	> 48,0 μgML^{-1}	Indução de apoptose Fragmentação de DNA aumentada e despolarização de membrana mitocondrial	56

cesses release NPs into the environment, including volcanic dust and degradation of biological materials[62]. Anthropogenic sources include manufactured NPs that are incorporated into various materials[62] and nonmanufactured NPs mainly originated from the burning of fossil fuels[63].

Silver is considered relatively toxic to humans [64] and to the biota[65]. Ag^{+} persists in the environment and can penetrate the cell membrane of living organisms. Until the 1970s, the photographic industry was the greatest anthropogenic contributor to environmental contamination with silver[66].

The increase in the commercial production of Ag NPs may lead to the environmental accumulation of silver species. Ag NP can be released into the environment during its synthesis, product incorporation, handling, and disposal of its end products[67]. When discarded into domestic and industrial effluents, Ag NPs can reach the conventional sewage treatment systems. Without any prior knowledge of appropriate treatments for this type of waste, effluents can be improperly disposed into the environment and disrupt aquatic ecosystems[68].

In effluents, Ag NPs may undergo transformations such as the acquisition of sulfur (S) radicals and subsequent formation of silver sulfide (Ag_2S), which may be stable enough to prevent S oxidation and subsequent release of Ag^{+}, depending on the environmental conditions.

Ag NPs can also incorporate into the sludge coming from the wastewater treatment process[69]. The sludge may be used as soil

Table 2. *In vivo* toxicity of Ag nanoparticles in mammals.

Animal	Size of the nanoparticles (nm)	Exposure route/ time	Dose	In vivo toxicity	Reference
Male and female Sprague-Dawley rats aged 8 weeks	18	Subchronic inhalation/90 days, 6 h/day	0,7 x 10^6,1,4 x 10^6,2,9 x 10^6 particles/ cm^3	No alteration in the micronucleus was observed. The test was performed in erythrocytes of rats of both sexes.	57
Wistar rats aged 10–12 weeks	15–40	Intravenous/ injection every 5 days	4, 10, 20, and 40 $mgkg^{-1}$	Induces DNA damage (assessed by the comet assay) in blood cells, increased liver enzyme levels at a dose of 40 mg, hematological abnormalities at doses of 20 and 40 mg, and oxidative stress in blood plasma at a dose of 40 mg.	58
Adult male mice (C57Bl/6N)	25	Intraperitoneal/24 h	1000 $mgkg^{-1}$	Induces oxidative stress and neurotoxicity	59
	20-100	Intravenous/28 days	2 and 6 $mgKg^{-1}$	Immunotoxic potential	40

fertilizer[70] or be incinerated[18] and thus release the silver back into the environment. Therefore, the fate of the sludge will affect the amount of Ag NPs discharged into the environment.

After entering the environment Ag NPs may undergo several modifications that will affect their transport, fate, and potential toxicity. Such modifications should be accounted for when assessing the degree of environmental impact caused by Ag NPs.

Behavior and transformation of Ag NPs in the aquatic environment

The behavior of NP depends not only on its characteristics but also on its interaction with abiotic and biotic environmental factors, which will determine the bioavailability and behavior[71]. In addition, it should be considered that after contact with the environment or living organisms NPs may be present in a free form or in clusters[72] (Figure 3).

It is known that Ag NPs exhibit different behaviors in distinct environments and in different culture media used in toxicity studies. The pH, stability of ionic strength, concentration, and type of organic material are some factors that will influence the behavior, bioavailability, and toxicity of Ag NPs[74].

In aquatic ecosystems, Ag NPs may undergo several changes that will interfere with their transport, dose (loss of charge), and nature of exposure (clustered or dispersed forms)[75]. According to Bradford et al. (2009)[74] Ag NPs tend to stabilize, precipitate, and accumulate in the sediment of aquatic ecosystems with high ionic strength and may react with inorganic and organic ligands such as S radicals, chlorine, and organic matter in environments where they are not thermodynamically stable[76,77,78].

The interactions between Ag NPs and natural organic matter or biological macromolecules will affect their dispersion and surface characteristics[79]. Thus, aquatic environments can aggregate Ag NPs and affect their behavior, transformation, and environmental impact.

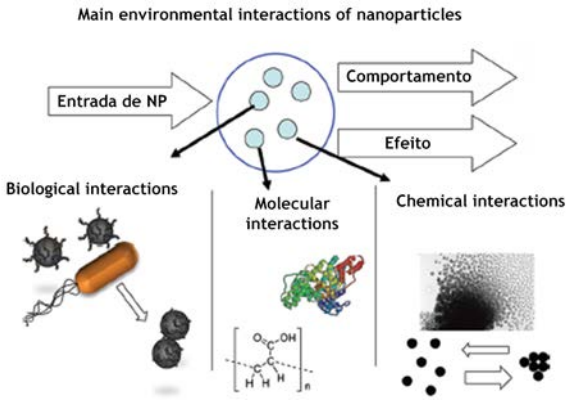

Figure 3. Potential environmental transformations of nanoparticles. Adapted from Lowry et all[73].

Other important factor that needs to be taken into account is that industrialized Ag NPs are usually stabilized with organic compounds (core–shell-type structures) by adsorption or by covalent bonds before they enter the environment[80]. Various types of coatings are used to stabilize Ag NPs, including carboxylic acids, polymers, polysaccharides, and surfactants. The steric stabilization of organic compounds due to adsorption may be limited because the ability of a polymer to stabilize NP will depend on the mass and conformation of the adsorbed layer and on the molecular weight distribution of the polymer[81]. According to Fábregas et al.[75], humic acids with a concentration greater than 10 mgL^{-1} tend to stabilize NPs by preventing aggregation.

Uncoated Ag NPs can be electrostatically stabilized against aggregation because of their negative surface charge, and repulsive forces can be electrostatically decreased by the presence of counter ions in the solution[82]. Therefore, the surface charge of NPs is influenced by electrostatic forces and is closely related to the state of deposition and aggregation.

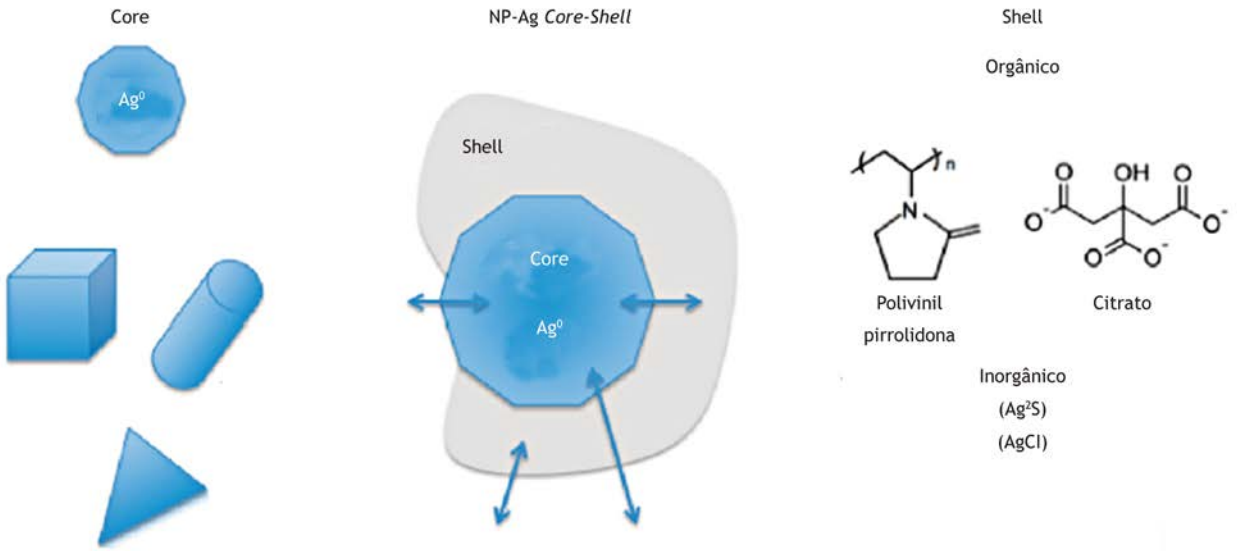

Figure 4. Core-shell structure of Ag nanoparticles, which can be released into the environment. Adapted from Levard[85].

The ion concentration in aquatic environments can alter the stability of Ag NPs. The ionic strength ranges from approximately 1 mM to 10 mM in freshwater and up to 700 mM in saline environments. Ag NPs tend to be unstable in these environments and form organic and inorganic species, and this instability may affect their mobility, bioavailability, and toxicity[83,84]. In aquatic environments, one of the greatest problems involves Ag NP oxidation and the formation of Ag^+. Ag^+ can form complexes with a weak base or organic matter, and these complexes can lead to the formation of Ag^2S, silver chloride (AgCl), silver carbonate ($AgCO_3$), and complexes with natural organic matter[82] in these environments (Figure 4).

Based on the thermodynamic behavior, Ag_2S and AgCl are the most relevant inorganic species originating from the transformation of Ag NPs in the environment. In this sense, Ag_2S, AgCl, and core-Ag are the most common species in freshwater environments, whereas AgCl and core-Ag^0 are the most common species in brackish environments[82].

From an environmental standpoint, the dissolution of Ag NPs in the presence of chloride ions appears to be related to the Cl/Ag ratio. In marine environments, where the Cl/Ag ratio is high, AgCl (aq), $AgCl_2$, $AgCl_3^{2-}$, and $AgCl_4^{3-}$ predominate. In freshwater environments, where the Cl/Ag ratio is lower, AgCl often occurs and tends to precipitate[82].

Ag NPs and other silver species strongly react with S present in aquatic and atmospheric environments in both aerobic and anaerobic conditions. Furthermore, when assessing the solubility of silver under aerobic conditions, it is important to consider the presence of NPs in the form of silver oxides because they quickly dissolve in pure water and release Ag^{+}[82].

Bioavailability and toxicity of Ag NPs in aquatic environments

The bioaccumulation and bioavailability of NPs are the result of a combined set of factors such as the concentration, chemical and physical characteristics of NPs and of the environment, exposure route, and the biology and ecophysiology of the organisms involved. Thus, the bioaccumulation and bioavailability depend on the size, shape, chemical composition, load, area and surface structure, solubility, and aggregation states of NPs[12]. These properties suffer interference from the environment; therefore, NPs must be characterized in the culture media used in toxicology tests and in the environment[86].

Although the bioavailability of Ag NPs is not completely elucidated, it is known that Ag^+ is the form with a greater toxicological potential on aquatic ecosystems[87]. In such environments, silver may be free or interact with various organic and inorganic ligands and its speciation is influenced by the physical and chemical properties of the environment, which will determine its potential toxicity[88].

In general, the bioaccumulation and bioavailability of NPs are associated with their ability to interact with the external surface of an organism or to be internalized. There is evidence that Ag NPs can cross the cellular wall of some organisms. In this sense, through transmission electron microscopy (TEM), Lee[89] and Asharani[14] found that fish cells could internalize Ag NPs conjugated with organic compounds. Fábregas[90] and Xu[91] also observed the capture of Ag NP by bacteria through TEM, and these results corroborate the ability of Ag NPs to penetrate semipermeable membranes[89,92].

Another poorly studied process whereby Ag NPs can translocate across membranes is endocytosis[6], in which particles and molecules with sizes between 1 and 100 nm are engulfed by membrane invagination and transported across the cytoplasm inside vesicles.

Ag NPs used in commercialized products are usually encapsulated with organic compounds for better dispersion, and these functional groups can influence the translocation through the cell membrane or affect the bioavailability properties of NPs [82]. With regard to environmental conditions, pH, ionic strength, temperature, and concentrations of organic matter will affect the stability and aggregation of NPs and thereby affect their bioavailability[88]. TEM images in Figure 5 demonstrate the bioavailability of Ag

Table 3. Ecotoxicity of Ag nanoparticles in aquatic organisms.

Test organism	Size of the nanoparticles (nm)	Nominal Concentration/exposure time	Reference
Daphnia magna	57.6	121 μgL^{-1}/48h	109
Daphnia pulex	57.6	8.45 μgL^{-1}/48h	
Daphnia pulex	20–30	0.04 mgL^{-1}/48 h	103
Daphnia galeata	57.6	13.9 μgL^{-1}/48h	
Danio rerio (embrião)	5–20	5-100 mgL^{-1}/72 h	14
Danio rerio (adulto)	26.6	1.000 mgL^{-1}/48 h	105
Danio rerio (adulto)	5-46	0.19-0.71 nM/120h	110
Oncorhychus mykiss	3-4	10-20 mgL^{-1}/48h	111
Thalassiosira weisfflogii	60-70	0.2-103mM	102
Paramacium caudatum	30-40	39 mgL^{-1}/1h	94
C. reinhardii	25	0.1-10µM/1-5h	12
Pseudokirchneriella subcapitata	20–30	0.19 mgL^{-1}/96 h	103
Ceriodaphnia dubia	20–30	0.46 mgL^{-1}/48 h	93

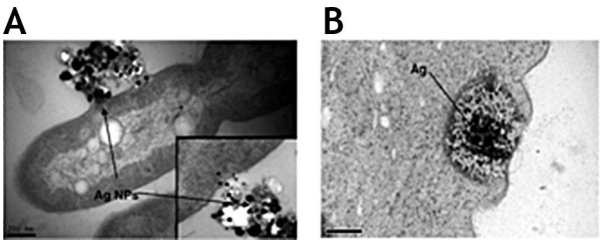

Figure 5. Transmission electron microscopy showing the internalization of Ag nanoparticles. A) Pseudomonas putida after 24 h of exposure to a suspension containing 2 mgL^{-1} Ag nanoparticles with 10 mgL–1 humic substance[90]. B) Trout gill tissue after 10 days of exposure to 100 mgL^{-1} Ag nanoparticles[92].

NPs associated with organic compounds such as proteins [bovine serum albumin (BSA)] and humic acids.

The solubility of Ag NPs will determine the degree of exposure of organisms to metallic silver (Ag^0), Ag^+, or silver complexes[78]. As mentioned earlier, the stability and solubility and therefore the toxicity of NPs are directly related to the concentration of organic matter. In this sense, Gao[93] found that the toxicity of Ag NPs in *Ceriodaphnia dubia* decreased in environments with a high concentration of humic substances and concluded that the decrease in toxicity was a result of a lower concentration of Ag^+ released by NPs in the presence of organic matter, i.e., a reduced bioavailability due to decreased solubility of silver. Similarly, Liu and Hurt[78] observed a decrease in the release of Ag^+ from NPs encapsulated with citrate, humic acid, and fulvic acid. However, Fábregas et al.[75,90] believe that the influence of organic compounds on the toxicity of Ag NPs goes beyond ion solubility. According to these authors, encapsulation by organic compounds can change the physical and chemical characteristics of NPs, thereby affecting their toxicity.

Another important factor to be considered is that NP aggregation determines the effective size of the particles to which the organisms are exposed and thus influences NP bioavailability and toxicity. According to Navarro[12], more aggregated NPs have a lower specific surface area and lower bioavailability and toxicological potential. In this sense, several studies have indicated that NP aggregation decreases toxicity to biota[74,81,94]. However, Ward and Kach[95] have observed that the increase in NP aggregation is associated with decreased toxicity in organisms that capture NPs through the membrane; on the other hand, the bioavailability increases in organisms that capture large food particles by ingestion.

Even in organisms that capture NPs through the membrane, the toxicity may not necessarily be related to the size but is related to the toxic elements carried by aggregates, which are capable of causing cellular damage. According to Reinsch [96], aggregated Ag NPs have a higher inhibitory effect on the growth of *Escherichia coli* than those dispersed in the medium, probably because of the radicals present in S aggregates.

The surface charge of Ag NPs is another important factor for cellular toxicity. In the case of bacteria with negatively charged cell walls, encapsulated Ag NPs with positive charges are responsible for growth inhibition. For this group of organisms, two mechanisms of toxicity have been proposed:

1) Oxidative stress as a result of the formation of ROS, which are potentially formed on the surface of Ag NPs[27, 97];

2) Interaction of Ag^+ released from NPs with the thiol group of enzymes and metabolically important proteins, affecting cell respiration and transport of ions across the membrane and culminating in cell death[87,88,98,99].

The toxicity of Ag NPs is also related to their oxidation state because the oxidation of Ag NPs and their subsequent dissolution in the form of Ag^+ are the main causes of toxicity of these compounds to different organisms[100]. However, in aquatic environments, the toxicity and bioavailability of Ag^+ are attenuated by the presence of S and by the formation of Ag_2S, which is relatively stable and insoluble[65,101].

Despite extensive research on the toxicity of silver to aquatic biota (Table 3), little is known about the effects of Ag NPs on these organisms. Some studies have indicated that the concentrations of Ag NPs found in aquatic environments did not affect the growth and photosynthetic efficiency of algae such as *Thalassiosira* sp.[102]. The authors found that toxicity occurred only when Ag^+ was released, whereas Navarro[13] observed that NPs were more toxic to *Chlamydomonas reinnhardtii* than their ionic form.

Data have shown that Ag NPs are liable to cause toxicity to invertebrates[103,104]; however, the toxicity is less than that caused by Ag^+[94]. The type of Ag NP, ionic strength, and concentration of organic molecules will influence invertebrate toxicity, similar to the effect observed for other groups of organisms. Kvitek[94] found that Ag NPs encapsulated with Tween 80, although more stable, were toxic to the ciliated *Paramecium caudatum*.

Previous toxicity studies have shown that Ag NPs with size between 10 and 80 nm affected the early developmental stages and survival of fish and also caused spinal deformity and cardiac arrhythmia[92,105,106]. Oxidative stress and accumulation of NPs in the gills and liver were also observed[92,106]. In general, the juvenile stages of fish were more susceptible to Ag NPs than to the same concentration of silver added in the form of $AgNO_3$. Moreover, Yeo and Yoon[107] found that aggregated Ag NPs were incorporated into the blood, skin, brain, and heart vessels of fish, whereas Ag^+ concentrated on the nucleus and organelles. Once accumulated, Ag NPs become available to other trophic levels and can therefore be incorporated into humans through the food chain[108].

Safety of manufactured nanomaterials: International regulation for Ag NPs

In Brazil, some efforts have been made to disseminate information and facilitate discussions between the society, health authorities, universities, and industries on the theme of toxicology. Moreover, the adequacy of national and international regulatory systems in evaluating products containing

nanomaterials has been widely questioned. This new positioning and increasing financial contributions have promoted the development of new research in nanotoxicology, with an aim of ensuring protection, health, and safety[112].

The number of products containing nanomaterials has steadily increased in the market from 30 in 2006 to 300 in 2011 and currently exceeds 1,000[113], generating a profit of 50 billion dollars in 2006[114]. It is estimated that approximately 1,120 tons of nanomaterials will be produced and commercialized in 2015[115,116]. These figures also attest the absence of minimum requirements for the regulation of nanomaterials. Potential health and environmental risks associated with the consumption and subsequent disposal of nanomaterials have become the subject of intense debate in the scientific community and a major concern of health authorities.

Thus, the protection of public health and the environment over market interests has become a big challenge for health agencies and the general public worldwide. Measures to inform the public on the risks of nanomaterials are essential because the Code for Consumer Protection in Brazil, which is regulated by Law 8078/90, has determined that it is a consumer right to protect health against potential risks arising from product consumption[117].

Therefore, there is an urgent need for the regulation of products containing nanomaterials by health authorities. Some countries in Europe and the United States have taken certain measures on this issue. The US federal agencies responsible for regulating the impact of Ag NPs on health and the environment are[88] the Environmental Protection Agency (EPA), the Food and Drug Administration [FDA; which regulates foods and products (including therapeutic products], and the National Institute for Occupational Safety and Health (NIOSH); the latter is responsible for the prevention of work-related diseases, risks, injuries, and deaths by determining the maximum occupational exposure limits [118]. EPA regulates the toxicity of Ag NPs through the following agencies: Toxic Substances Control Act (TSCA; which regulates chemicals and evaluates new products that may pose health and environmental risks before these products are commercialized) and the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA; which regulates pesticides and biocides[119]), with a focus on the regulation of products rather than the chemical compounds[120]. In April 2012, FDA published two new guidelines for food and cosmetics manufacturers, and these guidelines are open for public debate[114].

Based on all the control and regulation measures by US health agencies, the marketing of products containing nanomaterials has become more limited, and health and environmental risks have come to light.

Final considerations

The knowledge of the risks posed by nanomaterials to public health and the environment is important so that their production, marketing, and disposal can be performed properly and sustainably. The toxicity of Ag NPs is partly explained by the release of ions; however, more research on the subject is warranted to determine whether Ag NPs can directly cause toxicity. Scientific data on this topic are essential in setting environmental and public health policies and will be important as decision-making tools for governments to implement health regulation measures, invest in research, and promote further debate with a significant social impact.

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