Review

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Effects of silver nanoparticles on human health

Abstract: There has been a great deal of attention and research devoted on nanoparticels (NPs) over the last 10 years. From current knowledge in the field of nanotoxicology, it has become evident that the most NPs, if not all are more toxic than bulk materials. The rapid progress and developing has been leading to concerns about the potential risk associated with the use and application of NPs on human health and the environment. Silver nanoparticles (SNPs) are one of the most available and commercially distributed nanomaterials around the world. In order to understand how human health can be affected by SNPs, quantification and detection of SNPs in biological systems have to be conducted in different models. It seems that respiratory and gastrointestinal systems as well as the skin are the major routes of SNPs penetration into the body. Research on SNPs toxicity is mostly conducted in vitro, and the available human and animal data are relatively limited. This review attempts to focus on the characterization and quantification of the potential harmful effects of SNPs on human health.

Keywords: gastrointestinal toxicity; genotoxicity and carcinogenicity; immune system toxicity; kidney toxicity; liver toxicity; lung toxicity; muscle toxicity; nervous system toxicity; reproductive and developmental toxicity; silver nanoparticles (SNPs); skin toxicity.

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Introduction

Silver nanoparticles (SNPs) refer to the metallic silver with a size of 1–100 nm. The most common sources of SNPs are inorganic salts (1). In certain applications, the antibacterial activities of SNPs are significantly higher than its equivalent metal salt (2). Based on the method of production, SNP molecules are varied in structure and architecture, from oval, triangular, hexagonal shape to nano-wire forms (3). SNPs can be synthesized by traditional methods as well as an alternative method so-called biogenic or green NPs synthesis (4). Recently, many bacterial species, fungi, algae and plants are employed to produce clean, nontoxic, biocompatible and environmentally friendly SNPs (5–9). The advantage of biogenic SNPs are that the molecule can be coated with proteins (secreted by microorganisms such as fungi) allowing them more stable in the aqueous solutions (10).

Antimicrobial uses and antimicrobial resistances of SNPs

SNPs are widely used as potent antimicrobial agents in cosmetic and hygienic products (11, 12). On the other hand, silver-containing materials can be employed to eliminate microorganisms (13, 14). Despite of frequently using, the mechanism action of nanoparticles (NPs) as bactericides in aqueous solutions and solid media is not well known. The antibacterial activity is caused by release of silver cation from the nano-structured surface (15). The high reactivity of NPs might be due to the large surface compared to the low volume ratio (16). In general, the antimicrobial activity of NPs is linked to their ability to alter the cellular permeability and produce reactive oxygen species (ROS) (17, 18). It seems that SNPs below 10 nm are able to penetrate into

cytoplasm and disrupt cellular metabolism and inhibit biochemical processes (19, 20). For instance, silver fungicides are able to destroy cell wall and membranes of fungi (21–24). Antimicrobial activities of SNPs are not limited to the bacteria and fungi, as SNPs are useful against other organisms like viruses (25). Besides, SNPs may be applied to reduce insect populations such as *Aedes* species because they have potential larvicidal activity (26).

SNPs have become one of the most commonly used NPs in commercial products (27). Colloidal solutions of SNPs directly bound to the solid surface of materials and inhibit the growth of highly multi-resistant bacteria such as *Staphylococcus aureus, Escherichia coli, Vibrio cholera* and *Pseudomonas aeruginosa* (19, 28–30). The studies on silver-doped titania nanoparticles showed that this particles exhibits high activity against *Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis* and *E. coli* bacteria (31, 32). It has been mentioned that SNPs have antimicrobial activities against antibiotic resistant bacteria, without conveying the formation of resistances that is one of the challenging problems with using antibiotics (33–35). However, it has to be indicated that the formation of resistances to NPs were identified and there might be a concern about increasing resistance of microorganisms against SNPs in the future (36, 37).

Wound dressings SNPs, are available in markets and relatively safe for human health (11). Silver is also used on medical devices which implanted in the body for long periods of time (38, 39). Currently, it has been used on dental materials (40). The antimicrobial activity of SNPs against the oral pathogenic species, *Streptococcus mutans* was investigated and the results were compared to a dental disinfectant, chlorhexidine. The results proved that SNPs are more efficient than chlorhexidine (41). SNPs also are employed for other purposes such as water purification and biosensors (42, 43). Most importantly, the antimicrobial activity of SNPs has been mainly occurred in one and pure microorganism and it seems that such kind of studies to show the impact of SNPs on complex microbial communities are needed.

Overview of SNPs toxicity

Nowadays, along with the rapid progress and development of NPs, is necessary to have guidelines and regulations to reduce the potential risk associated with the use and application of NPs on human health and the environment. As recommended by experts the safety data sheets for all NPs has to be prepared unless, the toxicity tests required by the regulatory entities to show that they are not toxic for human. In particular, only limited health effects of SNPs in humans have been documented so far and less is known about their environmental impacts (44, 45). It is plausible that SNPs can release into the aquatic environment, affect on the aquatic biota (46, 47) and possibly circulate in the food chain. For instance, it has been reported that SNPs have a developmental impact on the zebrafish embryos *(Danio rerio)* (48–51). Occupational studies are relatively limited and in a few studies, workers have been exposed to low levels of SNPs under the threshold limit values and for a short period of time (52–54). Thus, to fill this knowledge gap reliable epidemiological and eco-toxicological studies are required. Toxicity of SNPs are linked with several physicochemical properties such as size, the chemical nature, surface area, reactivity and charge, compositions and ease of aggregations. It is believed that small particles are more toxic than larger particles but, the particle size is not the only factor that determines NPs toxicity (55–58). The size-dependent toxicity of SNPs has been tested in vitro and in vivo. In both models, smaller SNPs exhibited more toxicity than large particles (59–61). The surface coating is another important issue that contributes to the NPs toxicity. Several physicochemical properties such as surface charge, differential binding and aggregation potential can be influenced by the surface coatings of silver nanoparticles. It seems that some uncoated SNPs are less toxic than coated SNPs (62). Current literature demonstrates the importance of releasing silver ions and its contribution to the NPs toxicity. However, this hypothesis not yet completely accepted (63). It seems that the acute toxicity of silver and silver related compounds is due to the released silver ions (49, 64), therefore the critical impact of exposure media on the SNPs toxicity has to be taken in consideration. High concentrations of chloride ions (Cl^-) can cause precipitation of silver ion in the media as reported in the performed experiments on zebrafish and fish gill cell line (64, 65). The authors then concluded that the levels of free Ag^+ in the absence of chelators would be much higher and consequently SNPs toxicity would be augmented (65). From another side of view, chelators may directly neutralize the ROS and ameliorate SNPs toxicity (66).

Human exposures to silver and silver-related compounds mainly take place through three different routes of exposure, including dermal, oral and inhalation and subsequently, SNPs accumulate within secondary organ targets including liver, spleen and brain (67). As a matter of fact, prediction of SNPs toxicity is largely influenced by volume of distribution in the body (68). There is a gender-related difference in the distribution and kinetic profile of SNPs in

mice (69). It has been shown that oral or intravenous administration of SNPs can cause gradual accumulation in the kidneys and brain (70, 71) and excretion from the body via feces and urine (72). SNPs after interring biological systems may undergoes biochemical transformation leading to the formation of secondary particles and this may lead to long harmful effects on human health (73–76). However, in long-term exposure, liver and spleen are the major site of SNPs accumulation and toxicity (Table 1). Finally, systemic argyria as the most prominent human clinical feature of colloidal silver ingestion has been reported (77).

Skin toxicity

It has been shown that SNPs in wound dressing, medical applications promote rapid wound healing of pig's wounds (78, 79). The proteolysis environment of the wounds treated with SNPs is characterized by reduced levels of metalloproteinase and enhanced cellular apoptosis. The skin absorption of SNPs was evaluated in vitro and in vivo. The results showed that the skin absorption of SNPs is low but, detectable (80–82). In our sub-chronic study, SNPs were locally applied on the back of guinea pigs once daily for 5 days per week over a period of 13 weeks. A close correlation between dermal exposure and tissue accumulations of SNPs were monitored (83) using transmission electron microscopy (TEM) and X-ray diffraction (XRD). Indeed, a time-course and dose-dependent effects of SNPs on the skin were seen. Moreover, decreasing dermis and epidermis thickness were along with the increased number of Langerhans cells, increased inflammation markers, decreased thickness of papillary layers, and increased dermis collagen levels (84).

Clinical safety data sheet of SNPs-based dressings are to some extent questionable (85, 86). It seems that nanocrystalline coated dressings are the most toxic SNPs-based dressings (86, 87). Acticoat® formula has been tested in a small clinical trial study and contradictory results have been reported (88). In a porcine model of wound healing, SNPs wound dressing promoted rapid wound healing (78) with no side effects. The potential cytotoxicity of SNPs in human epidermal keratinocytes (in vitro study) and penetrating ability in porcine skin has been assessed (in vivo study) by Samberg et al. (82). The authors used eight different types of SNPs and skin has been topically exposed for 2 weeks. The results have shown that SNPs were nontoxic when applied purely (82). The authors concluded that the toxicity of SNPs in human epidermal keratinocytes can be influenced by the residual contaminants in the solutions, and that the particles themselves may not have been responsible for increased cell death. In our studies during the acute test, dose-dependent histopathological abnormalities were seen in the skin. In addition, experimental animals that subjected to sub-chronic exposure, showed greater tissue abnormalities than the animals treated with single doses. It seems that colloidal solutions of SNPs have the potential ability to induce multi-organ toxicity in a dose- and time-dependent manner (84). Taken together, a clear correlation between dermal exposures, accumulation of SNPs and dose-dependent histopathological abnormalities in skin were found (Table 1).

Lung toxicity

In vitro studies revealed that different types of SNPs in a dose-dependent manner exhibited toxicity towards lung cell lines (62). The expression of gap junctional intercellular communication (GJIC) and connexin43 (Cx43) were increased in human lung adenocarcinoma cell line A549 and author suggested that Cx43 and GJIC may the targets of SNPs induce lung toxicity (89). In an in vivo study conducted in male and female rats lung function was evaluated and the results indicated that female rats were able to gradually recover from the lung inflammation, whereas the male rats in the high-dose group exhibited persistent inflammation throughout the 12-week recovery period (90). Acute and sub-acute exposures to SNPs induce mild pulmonary fibrosis and inflammation and persistent release of SNPs can lead to sub-chronic injury responses (58, 91, 92). Animal studies revealed that oxidative stress is involved in this process, triggering lung tissue damages (93). One of the most important factors that can affect on the SNPs lung toxicity is the rate of intracellular Ag ion release (94). The studies conducted with different size of SNPs have indicated that smaller SNPs (10 nm) is more toxic particles in human lung cells than larger SNPs (58, 95). Taken together, several factors can influence SNPs lung toxicity, including bioavailability, size, and surface of the coating as well as period of exposure (Table 1).

Gastrointestinal toxicity

Since, the gastrointestinal system represents an important route of entry of SNPs into the human body either directly through intentional ingestion or trough systemic circulation, the fate of SNPs after entering the gastrointestinal system is not yet known. It has been shown that oral administration

Table 1 In vitro and in vivo toxicity of SNPs.

SNPs forms	Size of particles	In vivo data		In vitro data		Exposure		Organ	References
		Human study	Animal study	Primary cells	Cell line	Route of exposure	Period of exposure		
	15–40 nm		Wistar rat			Intravenous	Sub-acute	Liver	(1)
				Human liver cells				Liver	(2–4)
	<100 nm			Rat liver microsomes				Liver	(5)
(SiO(2)-NPs)	50–400 nm				Huh7 cells			Liver	(6)
	2.5–150 nm		Sprague-Dawley rat			Inhalation	Sub-acute	Liver, CNS	(7)
PS-NPs	7–10 nm				HepG2			Liver	(8)
Colloidal solution	Sizes <100 nm		Hartley albino guinea pigs			Dermal	Acute and sub-chronic	Liver, spleen, kidney, muscle, skin	(9–11)
	52.7–70.9 nm		Sprague-Dawley rats			By oral	Sub-acute	Liver	(12)
PVP-coated	<100 nm			Cerebellar granule cells (CGC)				CNS	(13)
SNPs	60 nm		Sprague-Dawley			By oral	Sub-acute	GI	(14)
	2.68–30.38 nm				AML cells			IS	(15)
Colloidal solutions	1–2.5 nm	A case report study			PBMCs	By oral		IS, CNS	(16, 17)
	Small size				Human lung cells			Lung	(18, 19)
	30–50 nm				A549 cells			Lung	(20)
Citrate-coated	10 nm		Male CD1-mice			IV	Sub-acute	R&D	(21)
SNPs	6.95–8.85 nm		Sprague-Dawley rats			By oral	Sub-chronic	R&D	(22)
	5–20 nm		Zebrafish					R&D	(23)

SNPs properties, experimental conditions, rout and period of exposure and target organ of toxicity are shown. Abbreviations: Huh7 cells, hepatoma cell line; HepG2, human liver hepatocellular carcinoma cell line; AML cells, acute myeloid leukemia; PBMCs, peripheral blood mononuclear cell; A549 cells, adenocarcinomic human alveolar basal epithelial cells; IV, intravenous; CNS, central nervous system; GI, Gastrointestinal; IS, immune system; R&D, reproductive and developmental systems.

of SNPs exhibit toxic effects (96, 97). In one study, a dose-dependent increased accumulation of SNPs in the lamina propria in both the small and large intestine, in the tip of the upper villi, the ileum and the protruding surface of the colon has been reported (98). In another animal study, SNPs were labeled with the silver radioactive isotope and administered intra-gastrically to pregnant female rats. Then the accumulation of SNPs in the rat fetuses was evaluated. The data demonstrated that SNPs can be penetrated through the placenta into the fetus body and accumulate in the fetus's liver, blood, brain and muscles (99). Penetration of SNPs from the intestinal loop to the other organs has been also reported (100). It is clear that SNPs are able to penetrate from the gastrointestinal tract into the human body and accumulating in the other organs (Table 1) to prove the local and systemic effects of SNPs on gastrointestinal system more human and experimental data are required.

Liver toxicity

In vitro study with human liver C3A cell line revealed that SNPs elicited the maximum level of cytotoxicity [half maximal inhibitory concentration of 2 μg/cm(2)] (101). Liver is a main target organ of chemical detoxification and toxicity (Table 1). It has been shown that SNPs can be accumulated in the liver after inhalation exposure (102). Liver biomarkers such as aspartate amino transferase (AST), alanine aminotransferase (ALT) and gamma-galactosyltransferase and histopathological parameters after SNPs administration were elevated (103). In accordance, the activities of several cytochrome P450 (CYP) enzymes such as CYP1A, CYP2C, CYP2D, CYP2E1 and CYP3A were inhibited by SNPs exposure (104, 105). It seems that SNPs are able to induce oxidative stress and cause cell damage and apoptosis in human liver cells trough different mechanisms (106–108). Cytoplasmic vacuolization and hepatic focal necrosis were seen after SNPs exposure (109). In our study, necrosis were observed only at the highest SNPs concentrations (10,000 μg/mL) (84). Toxic concentrations of SNPs are linked with induction of apoptosis and increased micronucleus formation and chromosomal damage (110).

Kidney toxicity

As the kidneys are the major organ of drug elimination, at the same way they might be potential targets of SNPs toxicity (Table 1). SNPs can be accumulated in the kidneys in a dose-dependent manner as reported by Kim and coworkers (111). Some medical devices that are loaded with SNPs can release silver ions (Ag^+) gradually, and then it can translocate into the blood circulation and accumulate in the kidneys (112). In response to SNPs exposure, proximal convoluted tubule degeneration, capsular and membranous thickening and mesangial abnormality have been reported (111). In our study, a clear relationship between dermal exposure and accumulation of SNPs in the kidneys was observed. After evaluation of 28 kidneys of treated animals and comparing the levels with the control group, six major toxic responses were recorded. Histopathological data showed inflammation, adhesion to Bowman's capsule, proximal convoluted tubule degeneration, capsular thickening, membranous thickening and increased mesangial cells in SNPs treated animals (83). It seems that more cautions and special attention have to be devoted to long-term using of SNPs in medical applications.

Muscle toxicity

In an occupational study, a group of workers was exposed to silver compounds. During experiments, an increasing in the N-acetyl-B-D glucoseaminidase (NAG) level and decreasing in the creatinine clearance has been observed (113). In our dermal study, the histopathological data confirm the toxic effects of SNPs on muscles (83). It seems that colloidal SNPs have the ability to create a dose-dependent toxic response in this organ. We found that both small and large sizes of SNPs were able to distribute in the muscles and induce muscle toxicity using transmission electron microscopy (TEM) and X-ray diffraction (XRD) (83). In agreement with us, muscular effects of SNPs have been reported in the other studies (114, 115).

Nervous system toxicity

Accordingly, the role of glutamatergic N-methyl-d-aspartate receptor (NMDA) in SNPs-evoked neurotoxicity has been investigated and the authors concluded that activation of NMDA is involved in the SNPs neurotoxicity (116). It was also documented that SNPs can cross the BBB and induces brain inflammation and neurotoxicity (117). It has been also reported that silver can be found within the BBB but could not pass through it (118). However, in vitro studies demonstrated that SNPs are toxic to brain cells (119). High levels of silver in plasma, erythrocytes and cerebro-spinal fluid along with epileptic seizures and coma after daily ingestion of colloidal silver have been reported

(120). This study also suggested that silver exposure can induce irreversible neurotoxicity which, eventually can lead to death. In contrary, no remarkable symptoms in the brain of rats that was exposed to SNPs via inhalation has been seen in another study (102, 109). Taken together, the current knowledge about central nervous system effects of SNPs are extremely limited and more clinical and experimental data are needed (Table 1).

Reproductive and developmental toxicity

The potential harmful effects of NPs on pregnant women and fetuses development are an important issue that has to be included in SNPs safety data sheets. The impact of SNPs on the proper functions of reproductive system has been tested in several studies (121, 122) (Table 1). The male fertility can be affected by NPs because spermatogenesis is very sensitive to these chemicals. The impact of dose, size and coating of SNPs to stimulate mouse spermatogonial stem cell proliferation was evaluated. According to in vitro studies, mouse spermatogonial stem cell viability was reduced in a size- and dose-dependent manner while SNPs coating had no effect on cell growth (122, 123). In one short term in vivo study, male CD1 mice were subjected to low concentrations of SNPs intravenously for 12 days. The data suggest that SNPs are not able to significantly reduce testis weight and sperm numbers but, it can alter the leydig cellular functions that lead to increase in the testicular and serum testosterone levels (124). In contrast, SNPs inhalation exposure has been shown to have no effect on the histopathology of the epididymis (109). Especially after inhalation exposure the systemic availability of NPs may be limited. In one study performed on pregnant CD-1 mice, SNPs intravenously administrated and after gestation days tissue samples were collected to evaluate silver content in different organs. The results demonstrated that SNPs were significantly accumulated in the visceral yolk sac and endometrium (125). In another study, reproductive and developmental toxicity of SNPs in both male and female rats has been investigated. No remarkable signs of reproductive and developmental toxicity in this study were reported (126) whereas, in zebrafish SNPs were distributed in the brain, heart, yolk and blood of embryos and induced several developmental abnormalities that restrict the survival chances of zebrafish embryos (48, 49). Taken together, there are insufficient information and limited acceptable studies on the reproductive and developmental toxicity of SNPs (Table 1).

Immune system toxicity

The in vivo nano-immune interaction studies are extremely limited and more caution is needed when NPs prescribed in biomedical applications. SNPs have been shown to be accumulated in the spleen of rats after inhalation exposure (102). A close correlation between dermal exposure and spleen accumulation was found in our study (83). The presence of SNPs at high concentrations in the respiratory system that was connected with local inflammatory responses has been reported. Systemic immune effects of SNPs have also been reported (127). SNPs larger than 100 nm can be readily phagocytized by alveolar macrophages (102, 128, 129) but smaller SNPs (<100 nm) tend to aggregate and inhibit alveolar macrophage activities (102). Thus, the smaller particles may be effective to treat inflammatory diseases (130). Further studies are necessary to determine whether high doses of SNPs can inhibit local inflammatory responses or not (92). However, application of SNPs in wound dressing formula could stimulate the immune system with no adverse effects (131). According to our results, SNPs can induce spleen toxicity. In animals that received low and medium concentrations of SNPs several signs of inflammation were observed (84) (Table 1).

Genotoxicity and carcinogenicity

The genotoxic effects of SNPs on calf thymus DNA have been reported. The results demonstrated that SNPs interaction with detergent induced genotoxicity (132). SNPs were able to interfere with the replication of DNA molecules and cause mutations (133) and to induce genotoxic activity in *Drosophila* (134). With subcutaneous administration, but not through intramuscular injection, tumor formation at the site of application has been observed (135–137). Toxic concentrations of SNPs are linked with the increased micronucleus formation and chromosomal damage (110). The in vivo administration of 60 nm SNP for 28 days has been conducted, but no statistically considerable genotoxic effects were seen (111). In an in vitro study, bulky DNA adducts and micronuclei formations in human cell lines were seen (138, 139). Interestingly, SNPs are more toxic to cancerous cells (140, 141) than normal cells and this may be valuable for developing anticancer drugs in the future studies. In this respect, human and animal studies are considerably limited and further studies are required to draw final conclusions. In conclusion, there is

inadequate evidence in humans for the carcinogenicity of SNPs, but there is limited evidence in experimental animals and in vitro studies.

Conclusion

SNPs have become one of the most frequently used NPs because of their potential antibacterial activities (85, 108, 142). In addition to binding affinity, several parameters such as size and surface area are recognized as important determinants of SNPs toxicity (55, 56). First of all, SNPs have to pass through the biological membranes. It seems that SNPs are small enough to penetrate through body barriers (143). Human exposure to silver and silver-related compounds mainly takes place through three different routes of exposure, including skin, gastrointestinal and lung. After absorption SNPs can be distributed in the blood and brain, and subsequently, to the other organs, such as heart and kidney. Smaller SNPs tend to be aggregated and inhibit the immune system, therefore their accumulation in the spleen may especially be effective in treating inflammatory diseases. Research on SNPs toxicity is mostly conducted in vitro with particles ranging from 1 to 100 nm. The available animal studies are relatively short term studies. On the other hand, research about the effect of SNPs on human health is limited. Sub-chronic dermal exposure can cause considerable accumulation of SNPs in the liver and lung (144). Animal available data have shown that SNPs causes histopathologic abnormalities in spleen, liver and skin (83). Our result clearly showed that muscles also are target organs of SNPs toxicity (144). It seems that colloidal SNPs have the ability to create a dose-dependent toxic response in several organs. In conclusion, there are very limited well controlled human studies on the potential toxicities of SNPs and further long term, wide range doses, preferably using multiple particle sizes, are needed to better characterize the risk of SNPs on human health. It is highly recommended to detect the role of shape and particle size on the toxicity profile of SNPs by different routes of administration in the future studies.

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Conflict of interest statement

Declaration of interest: The authors declare no conflicts of interest.

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