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Review Paper

A Review of Destructive Effect of Nano Silver on Human Health, Environment and Animals

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Abstract. Silver nanoparticles (AgNPs) are gaining attention from the academic and regulatory communities, not only because of their antimicrobial effects and subsequent product applications, but also because of their potential health and environmental risks. Nano-silver is used in an increasing number of products. Some of the applications have resulted in the concern of governments and the public, since little is known about the potential risks of nano-silver. It is hypothesized that the toxic effects of nano-silver are due to a combination of the specific properties of silver nanoparticles and the generation of ions from them. The main issue for future investigation is confirmation of our '0-hypothesis' that toxic effects of nano-silver are proportional to the activity of free silver ions which are released by the nanoparticles.

Key words: Nanotechnology, Nanoparticle, silver, health, environment.

1. INTRODUCTION

Nanometer sized silver materials are now used in various areas, including cloths, cosmetic materials, tooth pastes and washing machines (Lee et al., 2003; Gavanji et al., 2013). The major property of nano-silver materials is their antibacterial effect (Hamouda et al., 1999; Sondi and Salopek, 2004). However, there is no information regarding this antibacterial effect of silver nanomaterial when used by ordinary people. Furthermore, scientists worry about the toxicity of nanometer sized material, but little is known about its pathway into the cell. Found that rat and human alveolar macrophages had impaired function due to aggregates of ultrafine carbon particles, which may be linked to increased infection risk and decreased protection of sensitive lung cells, which were different from the common image of nano-material.(Yeo and Kang, 2008).

One of the substances used in nanoformulation is silver (nano-silver). It has been used since ancient times for jewelry, utensils, monetary currency, dental alloy, photography, explosives, etc. (Chen and Schluesener, 2008). Until the introduction of antibiotics, it was also used for its antiseptic activity, specifically in the management of open wounds and burns. Due to its antimicrobial properties, silver has also been incorporated in filters to purify drinking water and clean swimming pool water (Agency for Toxic Substances and Disease Registry [ATSDR] 1990, cited in World Health Organization. To generate nano-silver, metallic silver has been engineered into ultrafine particles by several methods, including spark discharging, electrochemical reduction, solution irradiation and cryochemical synthesis (Chen and Schluesener, 2008; Susan et al., 2009).

2. METHODOLOGY

Firstly, articles regarding to nano technology and effects of silver nano particles on human, animals and environment were searched in several data bases available through UI (University of Isfahan) library website and Google scholar too. Then they were reviewed during 4 months and important points related to the effect of silver nano particles on human, animals and environment were studied particularly.

2.1. The effect of silver nano particle on micro-organism

One of the most natural questions to ask when starting to deal with nanoparticles is: "why are nanoparticles so interesting"? The answer lies in the nature of and unique properties possessed by nanostructures. Nanoparticles are clusters of atoms in the size range of 1–100 nm (Gavanji et al., 2012). Reducing the particle size of materials is an efficient and reliable tool for increasing their biocompatibility. Furthermore, nano materials can be changed for more efficient applications in different fields such as bioscience and medicine (Kim et al., 2007). Elemental silver and silver salts have been used as antimicrobial agents for a long time. Silver nanoparticles (Ag-NPs) are one of the most commonly used nanoparticles,

most particularly serving as an antimicrobial agent for medical applications (Kandile et al., 2010). In fact, nanosilver is a new class of material with different physiochemical and biological characteristics such as increased optical, electromagnetic, catalytic properties and antimicrobial activity from the bulk materials. To produce nanosilver, metallic silver has been engineered into ultrafine particles by several methods, including spark discharging, electrochemical reduction, solution irradiation and cryochemical synthesis. Nanosilver particles are usually smaller than 100 nm and consist of about 20 to15000 silver atoms. Nanoparticles, including nanosilver may have different shapes such as spheres, rods and cubes. Furthermore, nanostructures can be generated as tubes, wires, and films (Wijnhoven et al., 2009). Ionic silver have some disadvantages such as its high reactivity which made it unstable and thus easily oxidized or reduced into a metal depending on the surrounding environment. In addition, ionic silver causes discoloration by itself or allows other materials to cause undesirable coloration and it does not continuously exert antimicrobial activity. Also, silver in the form of a metal or oxide, which is stable in the environment, is applied in a relatively increased amount because of its low antimicrobial activity (Park et al., 2006).

2.2. Effect on human health

Nano silver has biological properties which are significant for consumer products, food technology (e.g., food processing equipment, packaging materials, food storage), textiles/fabrics (e.g., antimicrobial clothing), and medical applications (e.g., wound care products, implantable medical devices). In addition, nano silver has unique optical and physical properties that are not present in bulk silver, and which are claimed to have great potential for medical applications (e.g., diagnostics, drug delivery, and imaging). As a destructive effect of nano silver on human health, the respiratory system represents a major port of entrance for nano silver. Sprays containing nano silver are already available on the market, indicating that this is a relevant exposure route. The distribution and disposition of nano silver in the respiratory tract depends on various factors including particle size and breathing force.

In addition, due to the small diameter of the nano silver, Brownian diffusion also determines deposition, resulting in a deep penetration of nano silver in the lungs and dispersion to the high lung surface area presented in the alveolar area. If nanoparticles are absorbed by the gastrointestinal tract, they will be transported directly to the liver through the portal vein. In general, the liver is able to actively remove compounds from the blood and transform them to chemical forms that can easily be excreted. However, no evidence exists for metabolism of nano silver by enzymes in the liver and the rest of the body.

The widest and best known use of silver preparations in medicine is as preferred antimicrobial agents for treatment of serious burns (Monafo and Freedman, 1987; Pruitt et al., 1998; Hoffman, 1984; Miller et al., 1990; Klasen, 2000). Atopical cream that contains 1% silver sulfadiazine plus 0.2% chlorhexidine digluconate in a water immiscible cream base is the most widely used product for human use and veterinary medicine, marketed as Silvazine in the USA (by Marion-Hoechst-Russell Laboratories, Kansas City, MO, USA) and as Flamazine in other countries, largely in the UK (Smith and Nelson Company; Roche), Canada and continental Europe. From the initial use of silver sulfadiazine creams, there has been more recent incorporation of the silver sufadiazine directly into bandages used on burned skin surfaces and similar large open wounds (Wright et al., 1998; Klaus et al., 1999). Use of direct current electricity to accelerate the release of Ag (I) from the covering into the damaged tissue and then penetration into the tissue has been shown beneficial (Matylevich et al., 1996; Chu et al., 2000), although this appears without wide use.

2.3. Human data

2.3.1. Clinical observations

Acticoat is a topical wound dressing consisting of a polyethylene mesh coated with nano-silver (average size 15 nm). There is one case report of silver poisoning after the use of Acticoat for treatment of severe burns to the legs (Trop et al., 2006). On day 6 post injury the patient developed a grayish discoloration, complained of being tired and having a lack of appetite. On day 7 silver levels in urine and blood were found to be elevated (28 and 107 mg.kg_1, respectively). Acticoat was removed and the discoloration of the face gradually faded and liver function test returned to normal values. Elevated blood silver levels were seen seven weeks post injury, but were hardly detectable after 10 months. These observed adverse effects may be associated with the release of Ag_ ions from the nano-silver dressing. Absorption of silver from Acticoat was confirmed in 30 patients treated in another study (Vlachou et al., 2007). However, despite measurable amounts of serum silver levels (median 59 mg.l_1) very limited changes in hematological or biochemical indicators of toxicity associated with the silver absorption were observed (Susan et al., 2009).

2.3.2. Central nervous system

Epileptic seizures and coma following daily ingestion of colloidal silver for four months were notified in one case report (Mirsattari et al., 2004). The authors suggest that silver caused these signs of irreversible neurological toxicity which eventually lead to death.

2.3.3. Liver

In the case report of Trop et al 2006, elevated liver enzymes (aspartate amino transferase, alanine aminotransferase and gamma-galactosyl transferase) after the use of Acticoat were reported. Levels returned to normal following cessation of exposure. The patient did not receive any other potentially hepatotoxic medication (Susan et al., 2009).

2.3.4. Immune system

Very limited changes in haematological or biochemical indicators of toxicity were associated with the silver absorption from Acticoat in humans (Vlachou et al., 2007), despite measurable amounts of silver in serum. Another case report possibly involving uptake of silver particles is the finding of small electron-dense particles, probably silver nanoparticles, in mast cells following 20 years of local acupuncture (Kakurai et al., 2003). The mast cells showed focal or partial loss of granule content suggesting degranulation (activation) associated with pruritus (itching) and an inflammatory reaction (Susan et al., 2009).

2.3.5. Skin

In a moist environment, silver is released from the Acticoat dressing (possibly as nanocrystals) and improve microbial control of the wound. Acticoat has been tested in small clinical trials with contradictory results. No adverse effects were found in the Tredget study, in which silver absorption was not assessed. Reported delayed reepithelialization and temporarily worse scars while in another study an increase in re-epithelization was found in meshed skin grafts. An additional case of delayed wound healing has recently been reported. However, all the studies were small scale and used different controls, thus interstudy comparison is hardly possible (Susan et al., 2009).

2.4. General Particle Inhalation Toxicity

Inhaled particles can lead to inflammation in the respiratory and cardiovascular systems, and known health effects include asthma complications, chronic bronchitis, and respiratory tract irritation and infections (Soto et al., 2007; Asgharian and Price, 2007; Ayres et al., 2008). Particle size and surface area are important determinants of inhalation toxicity. Numerous studies have demonstrated that airborne nanoparticles, regardless of chemical composition, pose a potential hazard to the lungs. Nanoscale particles are capable of penetrating further into the respiratory system than are larger, micrometer-scale particles, and they can also permeate through cell membranes of organisms and interact with subcellular structures. Nanoparticles' shape, crystal structure, and composition may present additional risk. For instance, Bang et al. asserted that crystalline particles seem to be more damaging to lung epithelial cells than are amorphous structures. In the studies performed by Duffin et al. in vitro and in vivo inflammation was not a function of nanoparticle mass, but of surface area. Also, nanoparticles may serve as carriers of pollutants that would otherwise not become airborne and enter human lungs. Nevertheless, uncertainty and disagreement still exist on whether the main cause for toxicity is related mainly to physical properties (namely size and shape), chemical composition, or a combination of both. Once inhaled, particles may deposit along the airways, from nasal and oral cavities to alveoli of the lungs, by impaction, sedimentation, interception, Brownian motion, or electrostatics. The efficiency of each mechanism depends strongly on size29 and on the local geometry and flow conditions within the respiratory system (Marina et al., 2010).

2.5. Silver, general toxicity

Since the most common forms of silver are elemental silver and the monovalent silver ion, the majority of the toxicological data on silver concern these two chemical forms of the element. Despite the widespread use of silver and silver ions in industry and for medicinal purposes, only limited information on silver toxicity is available. Existing environmental and human studies seem to demonstrate that some forms of silver, especially those that release free silver ions, are more toxic than others. This leads us to formulate the following hypothesis: Toxic effects of silver substances are proportional to the rate of release of free silver ions from them. Although acute toxicity of silver in the environment is dependent on the availability of free silver ions, investigations have shown that these concentrations of Ag_ ions are too low to lead to toxicity. Metallic silver appears to pose minimal risk to health, whereas soluble silver compounds are more readily absorbed and have the potential to produce adverse effects (Drake and Hazelwood, 2005). The wide variety of uses of silver allows exposure through various routes of entry into the body. Ingestion is the primary route for entry for

silver compounds and colloidal silver proteins (Silver, 2003; Susan et al., 2009).

2.6. Silver in the environment

Although silver is rare in the natural environment, concentrations may be elevated due to anthropogenic activities such as smelting, manufacture and disposal of photographic supplies, or coal combustion. It also leaks into the aquatic environment via municipal and industrial water treatment plants, which receive liquid waste from the photographic industry, the largest producer of silver contamination (Smith and Carson, 1977; Wen et al., 1997). From 1964 to2000 the world production of silver went from 7.4 to15.5 million kg (Silver Institute 2007). No numbers are available for more recent years, but uses of silver have changed significantly in the past decade. The rise of digital photography has resulted in an enormous reduction of the amount of film manufactured and processed annually, accompanied by a decrease in attendant silver emissions. This reduction (the photographic sector consumed 26% of the total silver demand in 1997) has been more than offset by the increased manufacture of electronic goods and the use of silver-containing conductive pastes and solders. Silver demand will likely continue to rise as silver finds new uses, particularly in the textiles, plastics, and medical industries, changing the pattern of silver emissions as these technologies and products diffuse through the global economy (Eckelman and Graedel, 2007).

The most abundant form of silver in the open ocean is AgCl2 (Bryan and Langston, 1992). Silver easily adsorbs to ferric compounds, clay minerals, etc. Furthermore, sorption by manganese dioxide and precipitation with halides reduce the concentration of dissolved silver in the water phase, consequently increasing the concentration in the sediment compared to the water. Only under reducing conditions will the adsorbed silver in the sediment be released resulting in either metallic silver or silver sulfide, which are both insoluble in water (USEPA, 1980). Silver thiolate complexes have been found in highly polluted waters. These complexes constantly exchange silver ions with each other and they also have the capability to transfer onto or off particulate matter and cells of organisms, besides the capability of forming silver sulfide (Bell and Kramer, 1999; Susan et al., 2009).

2.7. Bioaccumulation of silver

Bioaccumulation of silver has been investigated in several studies. Sanders and Abbe found that just 2 mg of silver.l^{-1} of water are enough for marine algae to accumulate significant amounts of silver (i.e. above the detection limit). Marine bivalve mollusks accumulate silver more strongly than algae and some mollusks can even accumulate silver from sediments. Oysters, gastrops and arthropods can all incorporate silver; the quantity in which this occurs depends on the biological availability of silver and age, size, sex, reproductive stage, general health and metabolism of the organism. Also, water temperature, salinity, dissolved oxygen, turbidity, and presence of other compounds may influence bioaccumulation (Presley et al., 1990). It was thought that silver accumulation results from the bioavailability of the free silver ion, but Reinfelder and Chang showed that AgCl was a factor contributing to an increase in silver uptake (Fortin and Campbell, 2000). Experiments with rainbow trout have shown that the uptake of silver takes place via a sodium-ion channel located on the branchial apical membrane (Bury and Wood, 1999). Research with the same fish by Hogstrand suggested that possible toxicity from silver accumulation in the liver was reduced by metallothionein, a protein that sequesters metals.

2.8. Silver, environmental toxicity

The acute toxicity of silver is dependent on its chemical form and the availability of free silver ions. Research has shown that with an aqueous concentration of only 1-5 mg.l^{-1} sensitive aquatic organisms and insects, trout and flounder can be killed (Bryan and Langston, 1992; Wood et al., 1994). Furthermore, accumulation of silver in species exposed to a slightly lower concentration of silver has lead to adverse effects on growth. With respect to marine environments, investigations have shown that the concentrations of bioavailable free silver ions are too low to lead to toxicity (Susan et al., 2009).

2.9. Animal studies

2.9.1. Clinical observations

Death has been observed in rats following exposure to very high doses of colloidal silver after intravenous administration (LD50, 67 mg.kg^{-1}) and after oral ingestion (1680 mg Ag.kg^{-1}.day^{-1} for four days. Following the intravenous injection of colloidal silver, rats died from lung oedema; while liver, spleen and kidney showed signs of brown discoloration. The cause of death following oral intake was not reported (Susan et al., 2009).

2.9.2. Central nervous system

Silver was found in the brain of rats systemically exposed to silver nanoparticles via inhalation (Takenaka et al., 2001; Ji et al., 2007), but no toxicity

endpoints were monitored in the brain. Furthermore, passage of the blood brain barrier (BBB) was also not investigated. According to a recent review on neurotoxicity of silver (not specifically nanosilver) (Lansdown, 2007), most animal studies indicate that after silver exposure silver was contained within the BBB but did not pass it (Susan et al., 2009).

2.9.3. Respiratory system

No distinct clinical and histopathological effects on the respiratory system of silver nanoparticles were seen during a 28 days inhalation study in rats (Ji et al., 2007). However, the study lacks specific examinations of the respiratory system such as respiratory rate, airway resistance, tidal volume, haemoglobin oxygen saturation as well as inflammation status. In the Takenaka study (Takenaka et al., 2001), silver accumulation was seen in the lungs of the rats (1.7 mg) of which 4% was still left after seven days, but again additional toxicity parameters were not included. Sung et al. (2008) performed a 90 days inhalation rat study (18 nm sized silver nanoparticles 6 h.day-1, 0.7, 1.4 and 2.9×10^6 particles/cm3) where they did show lung function decrease (including tidal volume, minute volume and peak inspiration flow), as well as inflammatory lesions in the lung morphology and effects on inflammatory markers (Susan et al., 2009).

2.9.4. Liver

Significant amounts of silver in the liver were observed after inhalation (Takenaka et al., 2001; Ji et al., 2007). At each time point analyzed, 9-21% of the nano-silver lung content was observed in the liver (Takenaka et al., 2001). Histopathology of the liver revealed cytoplasmic vacuolization in both sexes with a clear dose dependent increase in females. In addition, several cases of hepatic focal necrosis were seen in the high dose groups (Ji et al., 2007). No effect on the liver enzyme alkaline phosphatase (ALP) was observed. In contrast, repeated oral doses of 60 nm silver nanoparticles during 28 days did induce liver toxicity, as shown by increases in ALP and histopathological observations of dilatation of the central vein, bile-duct hyperplasia and increased foci (Kim et al., 2008; Susan et al., 2009).

2.9.5. Immune system

No treatment related effects on haematology and blood cell subset distribution (% lymphocytes, monocytes etc) was seen after inhalation of nano-silver particles. Of note, nano-silver particles were detectable in the spleen in the Takenaka study (Takenaka et al., 2001), but not in the Ji study (Ji et al., 2007). In the 90-days inhalation study of Sung, the presence of nanosilver particles in the lung may have induced a local inflammatory response in the high dose group. Parameters on potential systemic immune effects were not monitored in this study (Sung et al. 2008). In mice, application of a 1% nano-silver cream (96.1% isB50 nm) inhibited DNB-induced allergic contact dermatitis (Bhol and Schechter, 2005). It was found that the expression of two cytokines (TNFa and IL-12) was suppressed (histopathological staining) and apoptosis of inflammatory cells but not keratinocytes was induced. Similar concentration-dependent anti-inflammatory effects have also been seen in guinea pigs by the same group (Bhol et al., 2004; Susan et al., 2009).

3. CONCLUSION

Silver nanoparticles are gaining attention from the academic community, not only because of their antimicrobial effects and product applications, but also because of adverse health effects and environmental exposure scenarios. The fate of AgNPs in the environment and their short- and long-term health effects cannot yet be described in detail. (Marina et al., 2010)Several factors influence the ability of a metal to produce toxic effects on the body. The factors include the solubility of the metal, its ability to bind to biological sites, and the degree to which the complexes formed are sequestered or metabolized and excreted. For nano-sized particles additional parameters such as size and surface area are recognized as important determinants for toxicity (Ji et al., 2007).

Nanoparticles can pass through biological membranes. After administration, nanoparticles are small enough to penetrate even very small capillaries throughout the body. In conclusion, there are very limited well controlled studies on the potential toxicities of nanosilver. Additional long term, higher dosed studies, preferably using multiple particle sizes, are needed to better characterize the risk of the use of silver nanoparticles (Gavanji et al., 2012). There is not one form of nano-silver, and a more systematic approach is needed for determination of effects of different sizes of nano-silver. Because of its small size, nanoparticles can potentially pass through biological membranes and reach more and different organs and tissues in the body where the silver can exert its antibacterial effects. Since the prevailing view is that silver is relatively non-toxic (Chen and Schluesener, 2008), additional toxic effects, such as generation of oxidative stress, of nano-silver can be attributed to the nano-characteristics of the particle,

such as the large surface area and associated high reactivity.

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