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Toxicity of silver ions, metallic silver, and silver nanoparticle materials after in vivo dermal and mucosal surface exposure: a review

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Highlights

1. Silver is an ingredient in certain dermal and mucosal medical applications
2. Silver can deposit in the body as particles causing a discoloration called argyria
3. Silver is observed to have a low potential for skin irritation. Eye irritation and allergic contact dermatitis have been reported
4. Silver may cause genotoxicity, but additional data on its carcinogenic potential are required

Abstract

Silver is used in different applications that result in contact with skin and mucosal surfaces (e.g., jewelry, wound dressings, or eye drops). Intact skin poses an effective barrier against the absorption of silver. Mucosal surfaces are observed to be less effective barriers and compromised skin is often a poor barrier. Silver can deposit as particles in the human body causing a blue-gray discoloration known as argyria. Urine and feces are reported pathways of excretion. Acute human mortality has been observed following an abortion procedure involving the intrauterine administration of 7 g silver nitrate (64 mg silver/kg body weight). Localized argyria has been reported with exposure to silver ions, metallic surfaces, and nanocrystalline silver. Generalized argyria was observed with ionic and nanocrystalline silver in humans at cumulative doses in the range of 70 to 1500 mg silver/kg body weight. Silver is observed to have a low potential for skin irritation. Eye irritation and some cases of allergic contact dermatitis have been reported. Silver may cause genotoxicity, but additional data are required to assess its carcinogenic potential. Other reported toxicities include hepatic, renal, neurological, and hematological effects.

Keywords: Silver, nanoparticle, nanocrystalline, Acticoat, silver sulfadiazine, toxicology, dermal, eye, metallic, genotoxicity.

1. Introduction

Humans are exposed to silver from various sources. Silver is an antibacterial agent in the treatment of burn wounds, scalds, ulcers, and in the prophylaxis of neonatal conjunctivitis (Moore et al., 2015; Polk, 1966). Medical devices, such as catheters, transdermal drug delivery devices, acupuncture needles, and sutures, also contain silver (Lansdown, 2006). Other sources of silver exposure include amalgam fillings, self-medication, jewelry, deodorants, functional textiles, coins, tableware, coatings in refrigerators, and the workplace (Fluhr et al., 2010; Hipler et al., 2006; Miller et al., 2010; Nakane et al., 2006; Rongioletti et al., 1992; Schröder et al., 2012; Stefaniak et al., 2014; Tomi et al., 2004; Wollina et al., 2006; Yamamoto et al., 2012). Physical forms of silver are ions and metal. The metal encompasses nanoparticles and nanocrystalline coatings. The aim of this paper is to review the toxicity of silver following *in vivo* dermal and mucosal surface exposure. The endpoints genotoxicity and carcinogenicity are considered of very high severity. Therefore, genotoxicity and carcinogenicity data obtained using all *in vivo* exposure pathways (not only dermal and mucosal exposure) are considered as are *in vitro* data. In order to obtain all relevant journal articles for the current review, the following procedure was done. First, references were retrieved from the SciFinder (CAS, 2018) and Pubmed (Pubmed, 2018) databases, using combinations of appropriate search terms: “silver, nanoparticle, sulfadiazine, dermal, topical, mucosal, toxicity”. A total of 250 references were obtained and reviewed using this search strategy. Next, lists of references in relevant journal articles were reviewed to obtain literature that had not been obtained in database searches. An additional 50 journal articles were obtained this way. A total of 168 references were deemed relevant and included in the current article.

2. Absorption, distribution, metabolism, and excretion (ADME)

2.1. Absorption and distribution

A normal level of silver in blood was <1 µg/L, measured in 26 individuals who lived in the Melbourne metropolitan area. In liver, tissue levels were 0.03 and 0.05 µg silver/g in 2 deceased individuals (Wan et al., 1991). Daily dietary silver intake levels have been reported to be: 0.4 µg/day in a population from Italy

(Clemente et al., 1977), 7 µg/day, in Canadian women (Gibson and Scythes, 1984) and 27 µg/day in a population from the United Kingdom (Hamilton et al., 1973). WHO has reported that silver is occasionally found in drinking water at concentrations above 5 µg/L, and that daily intakes of silver are approximately 7 µg/person (WHO, 2008). Data on absorption of silver over intact skin, mucosal surfaces, and compromised skin are presented in Figure 1 and detailed in the following sections.

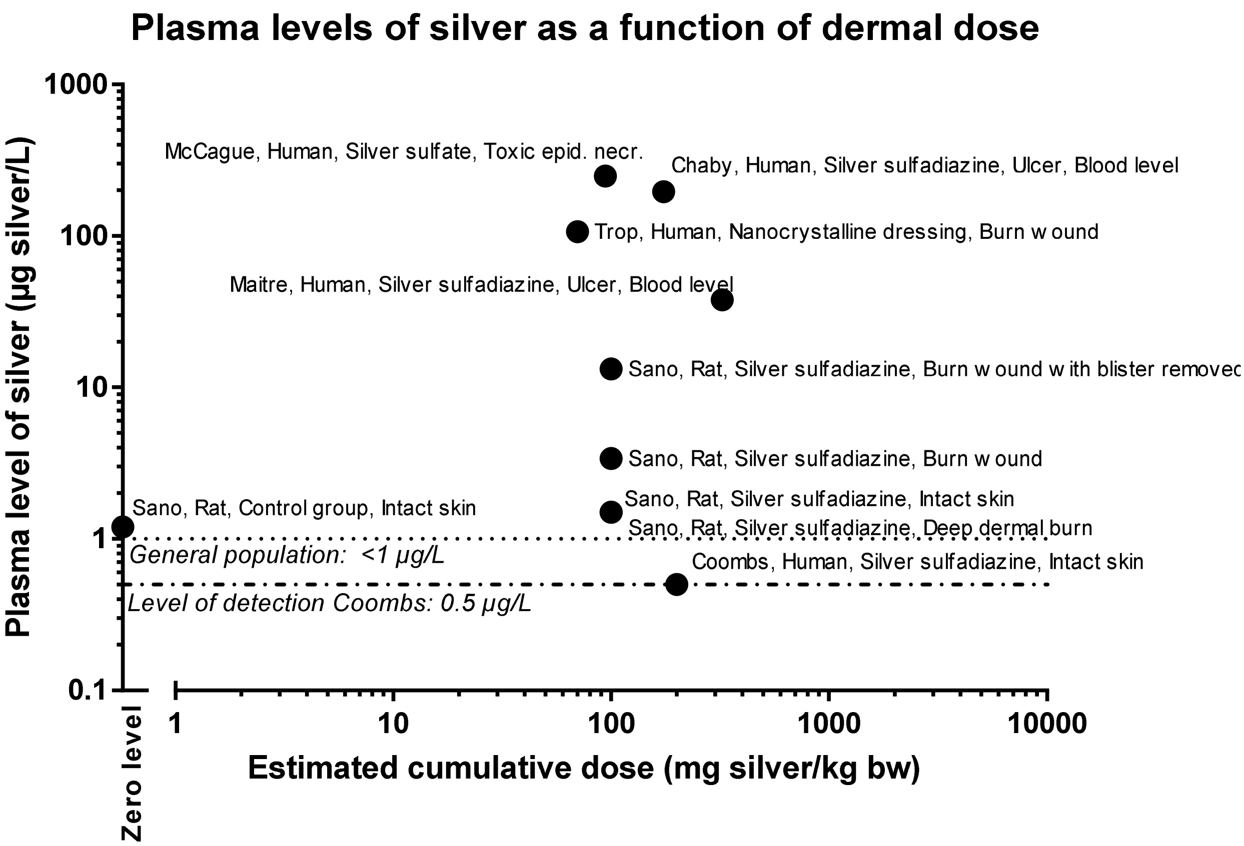

Figure 1. Levels of silver in plasma as a function of dose in humans and rats Legends designate: First author of the used reference, (animal) species, nature of the silver compound, and nature of the body lining exposed. For Maitre et al. and Chaby et al., blood levels were reported. Cumulative doses were estimated based on the number of doses, amount of silver in each dose, and body weights of 0.25 and 70 kg for rats and humans, respectively. The level of detection in Coombs et al. was 0.5 µg silver/L, illustrated by a vertical line on the graph. Levels of detection were not reported in any of the other references. "Coombs, human

silver sulfadiazine, intact skin" was reported as "no elevation of silver" and is depicted as being at the level of detection.

2.1.1. Absorption of silver over intact skin

Silver was not absorbed into the blood when human intact skin was exposed to 100 g of 1% silver sulfadiazine[1] cream per day for 2 weeks (~14 mg silver/kg bw/day) (Coombs et al., 1992). In guinea pigs, 2 mL of 0.24 M silver nitrate applied to 3.1 cm^2 of intact skin (~138 mg silver/kg bw) resulted in an absorption of silver ions of less than 1% (Wahlberg, 1965). In rats, a 1% silver sulfadiazine was applied to intact skin on 5 consecutive days (~20 mg silver/kg bw/day), yielding a serum level of 1.5 µg silver/L. Controls had a level of 1.2 µg silver/L. Levels of silver in liver, kidney, spleen, bone, and brain were equal in control and exposed animals (Sano et al., 1982). Silver from silver nanoparticles in the size range of tens to hundreds of nanometer in diameter penetrated into the human stratum corneum. Here it formed aggregates in deeper layers, likely slowing down penetration of silver into viable skin layers (Bianco et al., 2016).

2.1.2. Absorption of silver over mucosal surfaces

Silver has been described to cross the human eye mucosa following administration of silver nitrate (Karcioglu and Caldwell, 1985) and silver cyanide (Schlötzer-Schrehardt et al., 2001). For silver cyanide, this phenomenon has also been observed in rats (Rungby, 1986). Silver nitrate applied by intrauterine administration was fatal in one human, indicating uptake over the uterine mucosal surface. The dose was 7 g of silver nitrate (~64 mg silver/kg bw). In the woman this resulted in a blood level of 3480 µg silver/L, a urine level of 380 µg silver/L and in organ levels of: 8180 µg silver/kg (liver, tissue wet weight), 6100 (kidney), 2000 (heart), 148 (brain), 1400 (muscle), 140 (fat tissue), and 8200 (placenta). In the fetus organ

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[1] Silver sulfadiazine is a topical antibacterial agent in which the silver and sulfadiazine moieties are pharmaceutically active (Fox, 1975). The literature does not often specify if the mass concentration of SSD is weight/weight (w/w). However, for several products, the manufacturers' descriptions have included the (w/w) designation, for example, the Flamazine and Silvadene creams (Pfizer, 2016; Smith_&_Nephew_Healthcare_Ltd, 2011). In addition, the (w/w) designation is in compliance with FDA recommendations for reporting mass concentrations in topical creams (FDA, 2017).

levels were 840 µg silver/kg (liver, tissue wet weight), 400 (lung), 150 (muscle) and less than 10 µg/kg in kidney, heart and brain. The latter findings suggest that silver is able to pass the placenta (Reinhardt et al., 1971). A woman used silver-containing[2] nose drops for 10 years had a serum level of 63 µg silver/L, indicating that silver is absorbed over the nasal mucosa (Van de Voorde et al., 2005).

2.1.3. Absorption of silver over skin compromised by burn wounds

An 18-year-old man with a burn wound covering 96% of the body surface was treated with silver nitrate, resulting in blood and skin levels of 120 µg silver/L and 1,250 mg silver/kg, respectively (Bader, 1966). Silver sulfadiazine application to burn wounds resulted in serum levels of silver in the range of 2 to more than 200 µg/L and, in a deceased patient, silver was detected in the liver and kidney (Coombs et al., 1992). Burn patients administered silver sulfadiazine cream had a mean plasma level of 200 µg silver/L, and silver was detected in the corneal tissue, liver, and kidney at levels of 970, 14, and 0.2 µg silver/g tissue, respectively (Wan et al., 1991). When silver sulfadiazine cream was applied to rats, the absorption was low for a) normal skin (1.2 µg silver/L in serum), b) superficial dermal burn wound with blister (3.4 µg/L) and c) deep dermal wound (1.5 µg/L); notably, if the superficial dermal wound had the blister removed, silver in serum increased considerably (13 µg/L). A control group with no silver sulfadiazine application had a level of 1.2 µg silver/L. In all groups, silver was detected in liver, kidney, spleen, bone, and brain (Sano et al., 1982).

Nanocrystalline silver dressing[3] was applied to 6 patients with burns. A maximum serum level of 200 µg silver/L was measured at 9 days of treatment (Moiemen et al., 2011). Thirty burn patients treated with the dressing for 11 days had a median serum level of silver of 57 µg/L (Vlachou et al., 2007). In another burn

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[2] Argyrophedrine nose drops are described to contain 10 mg/mL efedrinelevulinate and 5 mg/mL silver vitellinate.

[3] Acticoat is a high-density polyethylene mesh with a core of rayon and polyester and coated with nanocrystalline silver. It is applied as an antibacterial dressing for the management of burns (Dunn and Edwards-Jones, 2004).

wound case, the application of nanocrystalline silver dressing for 7 days (~35 mg silver/kg bw/day[4]) resulted in a plasma level of 107 µg silver/L (Trop et al., 2006). In rats, dressings containing either silver sulfate or nanocrystalline silver were applied to burn wounds and changed every week. In weeks 3 and 6, the blood levels of silver were 136 and 33 µg/kg for silver sulfate and 62 and 168 µg/kg for nanocrystalline silver, respectively. In the spleen, kidney, and liver, the silver level was higher for nanocrystalline silver, compared with silver sulfate. Silver was also detected in the brain, testis, lung, heart, and muscle (Pfurtscheller et al., 2014).

2.1.4. Absorption over skin compromised by other wounds and scalding

A 64-year-old woman was treated for leg ulcers with 100 g 1% silver sulfadiazine cream every week. After treatment for 18 months, the blood level of silver was 38 µg/L (Maitre et al., 2002). A 61 year-old woman was treated for ulcers with 200 g silver sulfadiazine cream per day (~9 mg silver/kg bw/day). After 3 weeks of treatment, the level of silver in blood was 194 µg/L (Chaby et al., 2005). In 40 patients with chronic wounds treated with different silver preparations, serum silver was observed to correlate to wound area (Brouillard et al., 2018). Pigs with scalds were applied 1 g of 1% silver sulfadiazine cream for 48 h; Absorption of silver was less than 1%, but silver was detected in the eye, kidney, lung, stomach, adrenal, aorta, muscle, spleen, intestine, thyroid, and brain (Lazare et al., 1974).

2.1.5. Summary of the absorption of silver over skin and mucosal surfaces

Intact skin is observed to pose an efficient barrier against silver. Mucosal surfaces, including in the eye, are observed to pose a less efficient barrier. When skin is compromised by burns, scalds, or wounds, it is observed to be more penetrable; specifically, one study showed that uptake highly increased if the wound blister was removed. Following exposure, silver has been detected in all organs investigated. Detection in the brain indicates that silver crosses the blood–brain barrier.

[4] The dose was estimated using a content of silver of 1 mg/cm^2, application to 30% of the total body surface area (5700 cm^2), and three changes of the dressing during the treatment period.

2.2. Deposition of silver as particles in the body (metabolism)

Dermal metabolism of silver has been reported. Nanocrystalline silver and silver nitrate were administered to the skin of pigs. With the nanocrystalline form, silver at molecular weights corresponding to Ag, AgO, AgCl, $AgNO_3$, Ag_2O, and so-called silver clusters (Ag_{2-6}) were measured in the epidermis. With silver nitrate dosage, only AgO, AgCl, $AgNO_3$, and Ag_2O were observed (Nadworny et al., 2010). A substantial number of studies have described the deposition of silver as particles in the body (Supplementary material tables S1 and S2). Deposited particles observed in the skin were of brown or brown-black color at the microscopic level and differed in sizes: in the range of 10 to 1,000 nm (Kakurai et al., 2003; Matsumura et al., 1992; Sato et al., 1999; Suzuki et al., 1993; Tanita et al., 1985). In the eyes, the sizes of deposited particles ranged from 15 to 35 nm (Karcioglu and Caldwell, 1985; Schlötzer-Schrehardt et al., 2001). The anatomical localization of deposited silver-containing particles in the skin were especially a) in the surrounding eccrine glands (13 studies, Supplementary material tables S1 and S2), b) associated with elastic fibers (12 studies), c) in connection with collagen matrix/fibers (10 studies), d) surrounding small blood vessels (9 studies), and e) intracellular (8 studies). Regarding intracellular localization, this occurred inside fibroblasts (4 studies) and macrophages (2 studies) (Supplementary material tables S1 and S2). Subcellular localization was described as inside lysosomes and free in the cytoplasm (Rongioletti et al., 1992). In eyes, deposited particles were detected in the cornea, conjunctiva (Rungby, 1986), and other anatomical structures (Supplementary material table S1).

Deposited particles, in addition to silver, have also been reported to contain other elements. In generalized and localized argyria, deposited particles have been reported to contain a) silver and sulfur (Buckley et al., 1965; Schlötzer-Schrehardt et al., 2001); b) silver and selenium (Loeffler and Lee, 1987; Jan Aaseth et al., 1981); and c) silver, sulfur, and selenium (Bleehen et al., 1981; Karcioglu and Caldwell, 1985; Matsumura et al., 1992; Suzuki et al., 1993). The presence of sulfur in the deposited particles can be explained by the strong affinity of silver to sulfur by the Ag-thiolate binding (Massi and Santucci, 1998). The formed Ag_2S is chemically stable and highly insoluble in water (Liu et al., 2010). It has been suggested that sulfur in the deposited particles over time is substituted by selenium to form silver selenide (Massi and Santucci, 1998; Sato et al., 1999). Silver selenide is chemically more stable than silver sulfide and of even lower solubility. Additionally, the direct binding of silver to selenium in the enzyme glutathione peroxidase leading to the direct formation of the chemically stable and inert compound silver selenide has been suggested (Massi and Santucci, 1998). The serum level of selenium in patients with argyria was the most critical factor for the presence or absence of selenium within the silver-containing deposited particles, whereas no relation was observed for factors such as age; sex; the amount, duration, and route of silver introduced; or the different tissues and organs biopsied (Sato et al., 1999). The formation of the insoluble silver sulfide and silver selenide have been suggested to reduce the toxic effects of silver ions by reducing their biological availability (Massi and Santucci, 1998; Sato et al., 1999). Notably, a range studies, including oral exposure studies, case studies with acupuncture needle implantations, and some occupational studies, have also demonstrated the deposition of silver and selenium with chloride mercury, titanium, iron, nickel, sulfur, and osmium (Berry et al., 1995; Berry and Galle, 1982; Bleehen et al., 1981; Matsumura et al., 1992; Sato et al., 1999; Suzuki et al., 1993; Tanita et al., 1985; J Aaseth et al., 1981).

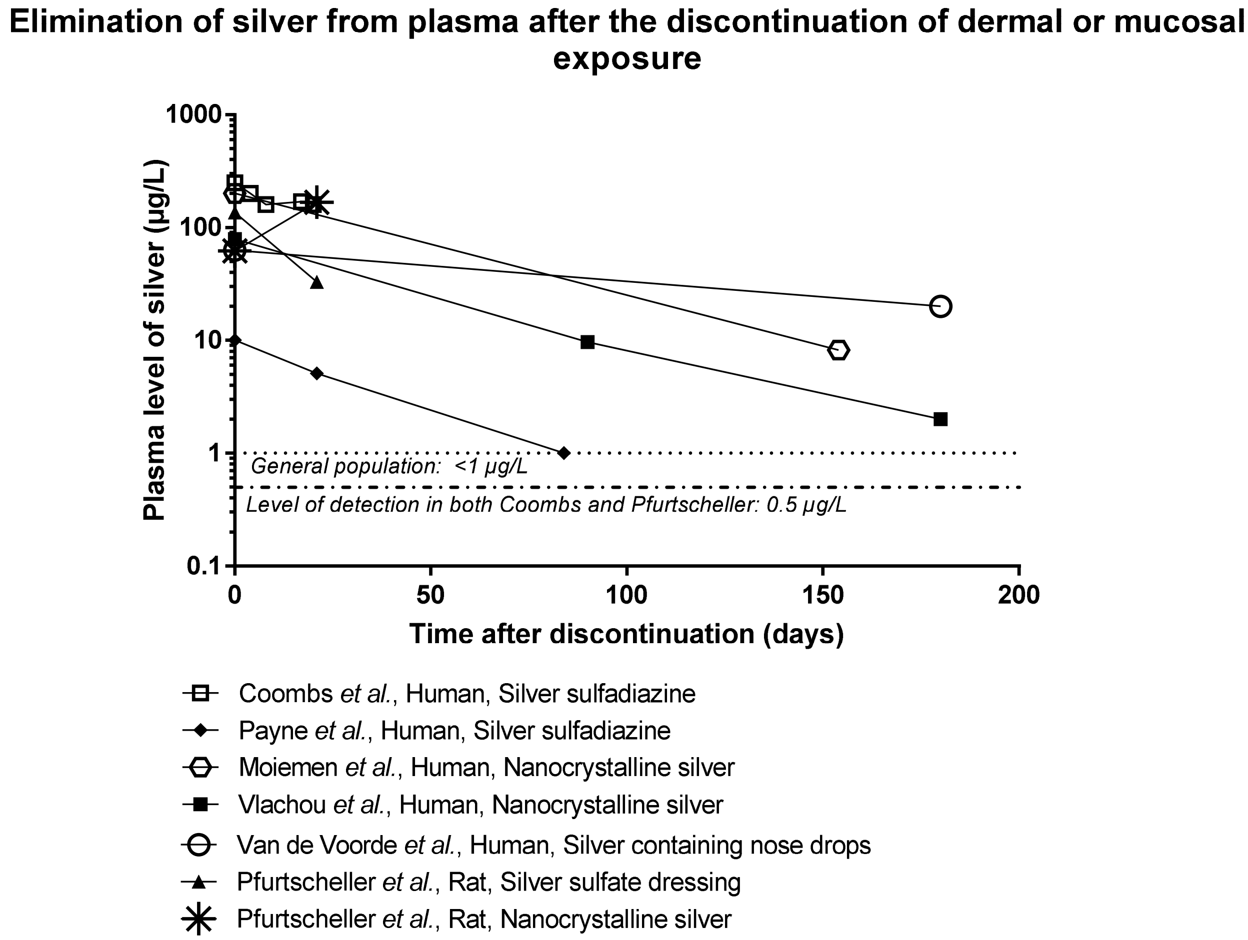

Figure 2. Elimination of silver from plasma after discontinuation of dermal or mucosal exposure in humans and rats Vertical dotted line illustrates the upper boundary of the normal plasma level of silver based on (Wan et al., 1991). The level of detection in both Coombs et al. and Pfurtscheller et al. was 0.5 µg silver/L, illustrated by a vertical line in the graph. Levels of detection were not reported in any of the other references.

2.3. Excretion

2.3.1. Time frame for the elimination of silver from blood

Figure 2 presents the literature on the elimination of silver from the blood. A 59-year-old man was treated for ulcers with 50 g of 1% silver sulfadiazine cream every second day for 5 months (~1 mg silver/kg bw/day). A plasma concentration of 10 µg silver/L decreased to 5.1 and 1 µg/L, 3 and 12 weeks after discontinuation, respectively (Payne et al., 1992). A woman used silver-containing nose drops for 10 years and had a plasma level of 63 µg silver/L that decreased to 20 µg/L 6 months after discontinuation (Van de Voorde et al., 2005). In burn wound patients treated with nanocrystalline silver dressing, the mean serum level of silver was 79 µg/L decreasing to 9.7 µg/L and 2.0 µg/L, 3 and 6 months after discontinuation, respectively (Vlachou et al., 2007). Patients with burn wounds were treated with silver nanocrystalline dressings for 9 days. This resulted in a plasma level of 200 µg silver/L that decreased to 8.2 µg/L 154 days after discontinuation (Moiemen et al., 2011).

Collectively, these data suggest that the process of silver elimination from the blood is prolonged, occurring over the duration of 200 days or more. This phenomenon could be explained by slow excretion or the continuous mobilization of silver from deposits in tissues.

2.3.2. Urinary and fecal excretion of silver

A normal urinary excretion rate was reported to be 2 µg silver/day (~1 µg/L) (Wan et al., 1991). In a patient where silver nitrate was applied for a third degree burn wound covering 96% of the body surface, the urine level of silver was 38 µg/L (Bader, 1966). In burn wound patients treated with silver sulfadiazine for various time periods, a urinary threshold level was found at a serum silver level of 100 µg/L: below this serum level, urinary silver was constantly low (<15 µg/L), and above this serum level, urinary silver was constantly high (>50 µg/L) (Coombs et al., 1992). In burn patients treated with silver sulfadiazine cream for 10 days, the mean plasma level of silver was 200 µg/L and urinary excretion rate was 100 µg silver/day (~50 µg/L) (Wan et al., 1991). In a 61-year-old woman, leg wounds were treated for 3 weeks with 200 g silver sulfadiazine cream per day. The urine level of silver was 148 µg/L (Chaby et al., 2005). In burn patients treated with 1% silver sulfadiazine cream for up to 70 days, the urinary peak silver excretion was 1,100 µg/day (~550 µg/L) (Boosalis et al., 1987). Human burns were treated with nanocrystalline silver dressing for 7 days, and a plasma level of 107 µg/L was accompanied by a urinary level of 28 µg/L (Trop et al., 2006). Pigs with scalds were applied a 1% silver sulfadiazine cream and silver was detected in bile (0.01 % of the dose), feces (0.02%–0.07% of the dose), and urine (0-0.02 % of the dose) (Lazare et al., 1974).

In summary, urinary excretion has been observed in humans. In addition, studies in animals have suggested fecal excretion as an accompanying pathway.

3. General toxicity - mortality and body weight loss

A pregnant woman had as an abortion procedure 7 g of silver nitrate (~64 mg silver/kg bw) applied in a 7% water solution by intrauterine administration and died 3½ hours later with symptoms of acute circulatory insufficiency. The postmortem examination showed erosion of labia paudendi, vagina, uterus, placenta and of the foetus. Histopathological findings were described as: Acute ingestion of the lungs, kidneys and central nervous system, as well as pulmonary edema and erosion of the uterine mucosa (Reinhardt et al., 1971). Burn wound patients were treated with 0.5% silver nitrate solution (2 kg/day/patient, ~90 mg silver/kg bw/day) for an unspecified period of exposure,[5] and no toxicity was observed (Bouterie and McLean, 1971). Guinea pigs were applied 50 mg of silver as a silver nitrate skin depot (~130 mg silver/kg bw); 8 weeks later, weight loss was observed. In comparison, mercuric chloride and cobalt chloride at the same molar dose caused death to more than half of the animal sample (Wahlberg, 1965). Guinea pigs were dermally exposed to a suspension containing 10–20 nm silver nanoparticles for a time period of 24 h. At the investigated doses, 0.04, 0.2, or 400 mg/kg bw, no effects were observed (Maneewattanapinyo et al., 2011). Similarly, no signs of toxicity were observed in rats following 24 h of dermal exposure to a suspension containing 10 nm silver nanoparticles at a dose of 2,000 mg silver/kg (likely per kg bw) (J. S. Kim et al., 2013).

[5] For one patient, the period was reported to be 56 days.

4. Argyria

Argyria has been described as blue-gray discoloration of the skin due to the deposition of silver. Argyria can be localized to the points of exposure (localized argyria) or, with higher exposure, be generalized and involve areas not directly exposed.

4.1. Localized argyria

A patient troubled by balanitis applied silver sulfadiazine cream intermittently for 15 years, resulting in localized argyria on the penis (Griffiths et al., 2006). A surgery wound was applied silver sulfadiazine and localized argyria was observed (Fisher et al., 2003). Ocular instillation of silver nitrate instillation caused argyria in the eye (Bartley, 1991), and the use of silver-containing eye drops for many years resulted in argyria of the lacrimal sac (Loeffler and Lee, 1987).

Regarding metallic silver, one silversmith had argyria in the fingers (Kamiya et al., 2011) and another in the fingers and arm (García-Martínez et al., 2016). Localized argyria was observed in jewelry manufacturers, in skin (Robinson-Bostom et al., 2002) and eyes (Tendler et al., 2017) following the occupational handling of silver (Nagano et al., 2016) and after exposure to mirror fragments (Hristov et al., 2011). A 40-year-old woman developed argyria following the accidental imbedding of an acupuncture needle 7 years earlier (Park et al., 2018). A teenage girl had toxic epidermal necrolysis involving almost 100% of the body surface. She was treated with nanocrystalline silver dressing for an unspecified period, and 4 years later, localized argyria was observed (Shaub et al., 2014). A 50-year-old silversmith had approximately 70 blue macules scattered on his face, limbs, and trunk. These contained silver, sulfur, chloride, phosphorous, silicium, aluminum, calcium, and potassium. The macules corresponded to sites where silver wires would puncture his skin (Rongioletti et al., 1992).

A range of cases have reported localized argyria but without testing for the presence of silver in the tissue, including cases with dermal exposure to metallic silver (Ferrara et al., 2018; Kapur et al., 2001; Morton et al., 1996; Palamar, 2010; Shall et al., 1990; Sugden et al., 2001; Utikal et al., 2006; van den Nieuwenhuijsen et al., 1988) and in the eye after exposure to silver nitrate-coated soft lenses (Hau and Tuft, 2009). In addition, localized argyria was suggested in a burn patient treated for 10 days with nanocrystalline silver dressing (~2 mg silver/kg bw/day[6]) (Zweiker et al., 2014).

4.2. Generalized argyria

4.2.1. Cases in which generalized argyria was concluded based on the detection of silver in the discolorations

Generalized argyria developed in a patient with oral ulcers who had her tongue painted with 10% silver nitrate repeatedly for 1 year (~0.2 mg/kg bw/day[7]) (Lee and Lee, 1994). Another case was in a 58-year-old woman who, because of nasal obstruction, had been using silver vitellinate-containing nose drops for 10 years: her serum level was 63 µg silver/L (Van de Voorde et al., 2005). Another case with the use of silver-containing nose drops was reported by (Massi and Santucci, 1998). A 58-year-old man with chronic laryngitis had self-administered silver over 15 years in the form of a spray containing argento-mercapto-3-hydroxy-2-propane-sodium-sulfonate and m-acetyl-amino-p-hydroxy-phenyl-sodium-arsenate. The combined cumulative intake of the 2 compounds was estimated to be 360 g. A diffuse blue-gray coloration of the skin was noticed. The patient died of small cell anaplastic lung carcinoma, and at autopsy, a frank dark coloration of the renal cortex and choroid plexuses was observed. Silver-containing black granules were detected in all investigated organs except the brain parenchyma (Gherardi et al., 1984). Other cases in which generalized argyria were confirmed by the detection of silver in biopsies were a case of using a silver foil-coated mouth refresher over a duration of 20 years (Sato et al., 1999), and a case in a plating factory employee (Matsumura et al., 1992).

[6] The dose was calculated based on an expected release of 1 mg silver/cm^2 and a bw of 70 kg. The dressing was changed every 3 days.
[7] The dose was estimated using an assumed volume of 0.5 mL applied twice a week.

4.2.2. Cases in which generalized argyria was diagnosed but not proven by tissue detection of silver

A 46 year-old woman was extremely pigmented after using silver nitrate for bleeding gingiva 3 times per week for 26 months. In a liver biopsy, silver colored pigment was observed in portal areas and around central veins. Over the next 2 years, no substantive decrease in skin pigmentation level was observed. At subsequent abdominal surgery, the pancreas, stomach, hepatic capsule, spleen, intestines, and peritoneum were all discolored in a manner similar to the skin. The pancreas was, by far, the most pigmented and appeared silver colored. Gastric biopsy revealed deposition of what was designated as silver granules in the connective tissue (Marshall and Schneider, 1977). Nose drops containing 20% silver iodide 6 times a day for 9 years caused generalized argyria in a 69 year-old man (~0.5 mg silver/kg bw/day[8])(Rich et al., 1972). Another case of argyrosis was in a 45-year-old male who had performed intranasal administration of 10% silver nitrate, or so-called Argyrols,[9] for 17 years, using a total volume of ~30 mL/week (i.e., combined volume of the 2 preparations) (Kleckner Jr., 1949). A 25-year-old woman with severe generalized dystrophic epidermolysis bullosa was, since early childhood, treated with 1% silver sulfadiazine cream and had developed generalized argyria. The serum level of silver was 283 µg/L (~0.1 mg silver/kg bw/day) (Flohr et al., 2008). A 23-year-old patient with the same condition was treated, since birth, with applications of silver sulfadiazine cream to denuded areas 2–3 times a day (~0.1 mg/kg bw/day), resulting in argyria with a serum level of 130 µg silver/L (Browning and Levy, 2008).

A 58-year-old man had his throat painted with mild silver protein repeatedly from the age of 3 to 12 and occasionally used silver protein-containing nose drops. Generalized argyria developed in childhood, but as he grew up, the abnormal color became less apparent (Pariser, 1978). A 81-year-old woman had developed generalized argyrosis 40 years earlier when treated for sinusitis with Argyrol for 2 years (Rosenblatt and

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[8] The dose was estimated using an assumed nose drop volume of 0.05 mL applied 6 times per day.

[9] So-called silver protein in the form of Argyrol, according to Lancaster, was introduced in 1902 and produced by extracting gliadin from wheat and treating it under pressure in an autoclave, obtaining a white granular precipitate reported to be the nature of a vitellin. When this protein is combined with silver, the resulting product is a dark brown powder containing 30% metal. According to other accounts, the so-called vitellin is obtained from serum albumen by hydrolysis (Lancaster, 1920), and it has been reported that the metal constitutes only 20% of the preparation (Marshall and Neave, 1906).

Cymet, 1987). Generalized argyria also occurred in a 42-year-old man who had used 2, 10 mL bottles of silver-containing nose drops weekly over the past 4 years to ameliorate allergic rhinitis. One drop contained 0.85 mg of silver protein (Tomi et al., 2004).

Regarding nanosilver, a 17-year-old male with 30% mixed depth burns was treated for 1 week with nanocrystalline silver dressing (~35 mg silver/kg bw/day). Generalized argyria was suggested based on a grayish discoloration of the face. The plasma silver was 107 µg/L (Trop et al., 2006). A patient with toxic epidermal necrolysis covering 70% of the body surface was treated with 8,000 cm^2 of a silver sulfate-containing dressing[10] for 7 days. Argyria covering a large part of the body surface was reported. A peak serum level of silver was 249 µg/L. The patient developed multiorgan system dysfunction and eventually died (McCague and Joe, 2015).

4.3. Is argyria a transient or permanent condition?

Argyria has been described as a persistent condition. In one case, argyria in connection with the use of silver sulfadiazine cream did not diminish over 3 years (Fisher et al., 2003). Some cases, however, have observed argyria to be reversible. Localized argyria disappeared 3 years after the discontinuation of exposure to nanocrystalline silver (Zweiker et al., 2014), and generalized argyria following one week of nanocrystalline silver dressing was reversible (Trop et al., 2006). The insolubility of compounds of silver in combination with other elements, as previously described, might explain the irreversibility of the coloration of the skin in some patients with argyria (Sato et al., 1999).

4.4. Summary of argyria data

Localized argyria has been reported with exposure to silver ions, metallic surfaces, and nanocrystalline silver. Generalized argyria has been observed with ionic and nanocrystalline silver in humans at cumulative doses in the range of 70 to 1500 mg silver/kg body weight (Browning and Levy, 2008; Flohr et al., 2008;

[10] Mepilex Ag Dressing has been reported contain a silver sulfate preparation that releases silver nanoparticles into wounds (Gee Kee et al., 2013).

Kleckner Jr., 1949; Lee and Lee, 1994; Rich et al., 1972). Regarding serum silver levels associated with generalized argyria, these are in the range of 63–283 μg/L (Browning and Levy, 2008; Flohr et al., 2008; Trop et al., 2006; Van de Voorde et al., 2005). Humans in which no argyria was reported had silver serum levels in the range of 0–300 μg/L (Moiemen et al., 2011; Vlachou et al., 2007; Wan et al., 1991).

5. Contact dermatitis and eye irritation

5.1. Irritant contact dermatitis and eye irritation

In a controlled clinical trial with 24 patients on topical silver sulfadiazine with standard gauze dressings, no contact dermatitis was recorded (Genuino et al., 2014). No irritation was found in rabbits having 0.5 mL of a 21% 10 nm silver nanoparticle solution applied to 6 cm^2 of skin for 4 h (~16 mg silver/cm^2) (J. S. Kim et al., 2013). Pigs were applied with 20 and 50 nm silver nanoparticles at doses of 0.34 or 34 μg/mL/day for 14 days (~0.06 and 6 μg silver/cm^2). No gross irritation was observed, but microscopic and ultrastructural observations showed areas of focal inflammation at a high dose and intracellular edema at a low dose (Samberg et al., 2010). In rabbits, a 100 cm^2 dressing of cotton fabric containing a 2% silver nanoparticles dispersion was dermally applied. The silver preparation was classified as a barely perceptible irritant (Zelga et al., 2016). In rabbits, different silver salts were applied to the eyes. All investigated salts, namely, silver nitrate, silver ammonium nitrate, silver ammonium sulfate, and silver ammonium lactate, were found to irritate eyes (Calvery, 1941). Further, a 100 mg of 10 nm silver nanoparticles in 21% solution was applied to one eye of rabbits (~5 mg silver/cm^2). Following 3 days of observation, no signs of irritation to the cornea, iris, or conjunctiva were observed (J. S. Kim et al., 2013).

5.2. Allergic contact dermatitis substantiated by patch testing and animal data on skin sensitization

Silver metal disks and a silver nitrate solution were patch tested, each on the skin of 50 humans having hand dermatitis. Sensitivity was detected in one patient who was exposed to both silver nitrate and silver metal (Gaul, 1954) Ozkaya reported a case of allergic contact dermatitis from silver nitrate in a patch test marker (Ozkaya, 2009). A patient suspected of having a sensitivity reaction to silver sulfadiazine was found to be sensitive to silver nitrate (Fraser-Moodie, 1992). Positive patch tests for silver nitrate were observed in 2 out of 118 patients with oral lichenoid lesions topographically related to dental fillings (Laine et al., 1997). In patients with leg ulcers and contact dermatitis, silver nitrate was found to be an allergen in 12% of the cases (Jankićević et al., 2008). Contact dermatitis was associated with a positive patch test for silver in a 23-year-old man whose work involved weighing silver (Heyl, 1979). A case of persistent periodontitis was cured by replacement of all silver amalgam restorations. The patient had a history of developing a rash and swelling whenever she wore jewelry containing silver. A patch test for silver nitrate was strongly positive (Catsakis and Sulica, 1978).

Silver nanoparticles were tested in a guinea pig skin sensitization test, and 1 in 20 animals demonstrated discrete or patchy erythema, suggesting a weak skin sensitizing effect (J. S. Kim et al., 2013). In the same assay, a dressing of cotton fabric containing a 2% silver nanoparticles dispersion was classified as a grade II mild sensitizer (Zelga et al., 2016).

5.3. Cases in which contact dermatitis was reported but not categorized

A 35-year-old man was treated for a burn wound with silver sulfadiazine twice daily and developed erythema. Notably, he was also treated with silver sulfadiazine 3 years earlier (McKenna et al., 1995). Dermatitis was reported following exposure to metallic silver strands incorporated in silken and woolen fabric (Hollander, 1955). Allergic contact dermatitis to silver was reported in a jeweler (Agarwal and Gawkrodger, 2002).

5.4. Conclusion on contact dermatitis and eye irritation

Overall, silver is observed to have a low potential for skin irritation. Eye irritation has been demonstrated, and some individuals develop allergic contact dermatitis to silver.

6. Genotoxicity and carcinogenesis

Silver has been reported to bind to purine and pyrimidine bases in DNA (Goff and Powers, 1975; Luk et al., 1975; Sabbioni and Girardi, 1977), increasing the possibility of it interfering with the normal function of the genes.

6.1. Genotoxicity studies in vitro

Details of *in vitro* genotoxicity studies are presented in Supplementary material table S3. Overall, silver ions do not indicate mutagenic activity in bacterial assays. An exception is silver iodide, exerting a minor effect in the TA97 *Salmonella typhimurium* frameshift strain (Eliopoulos and Mourelatos, 1998). Silver nanoparticles did not indicate any mutagenic activity in *Salmonella typhimurium* frameshift and base-pair substitution strains (Cho et al., 2013; Guo et al., 2016; H. R. Kim et al., 2013; Li et al., 2012). However, a negative Ames test result for a nanoformulated compound must be taken with caution, because particles may not be able to penetrate the bacterial cell wall (Landsiedel et al., 2009).

In the comet assay, silver nanoparticles induced DNA strand breaks in different cell lines (AshaRani et al., 2009; Eom and Choi, 2010; Stephan Hackenberg et al., 2011; J. S. Kim et al., 2013; Souza et al., 2016). However, no effect was observed in the NT2 human testicular embryonic cell line nor in primary testicular cells from mice (Asare et al., 2012). Mouse lymphoma cells were incubated with silver nanoparticles and had increased DNA strand breaks following co-incubation with oxidizing enzymes (Mei et al., 2012). HK-2 immortalized human proximal tubule cells incubated with silver nanoparticles increased DNA strand breaks (Kermanizadeh et al., 2013). Silver ions were observed to increase the number of micronuclei in 2 cell lines

(Guo et al., 2016; Li et al., 2012). Several cell lines were incubated with silver nanoparticles and micronuclei levels increased in all but one (Kruszewski et al., 2013).

In chromosomal aberration assays, silver nanoparticles have been positive in 1 of 2 studies (Hackenberg et al., 2011; J. S. Kim et al., 2013). Regarding gene mutations in mammalian cells, silver ions and nanoparticles have exerted a positive effect in the mouse lymphoma assay (Guo et al., 2016; Mei et al., 2012). By contrast, silver nanoparticles of different sizes had no effect in the MEF-LacZ cell mutant frequency assay (Park et al., 2011).

In summary, silver ions and silver nanoparticles do not induce mutations in bacterial assays. By contrast, several studies have shown that silver nanoparticles cause primary DNA damage in different cell lines in the form of DNA strand breaks. In addition, oxidative DNA damage was observed when oxidizing enzymes were applied. Regarding chromosomal damage, there is an indication that both silver ions and silver nanoparticles have effects. Finally, silver nanoparticles may induce mutations in mammalian cells; however more studies are required for clarification.

6.2. Genotoxicity studies *In vivo*

Details of *in vivo* genotoxicity studies are presented in Supplementary material table S4. In jewelry workers exposed to metallic silver, DNA strand breaks increased in mononuclear leukocytes (Aktepe et al., 2015). Notably, jewelry workers in addition to skin exposure may also be exposed to silver fumes. Regarding nondermal pathways, rats were intravenously injected with 20 or 200 nm silver particles. Micronuclei levels were increased in bone marrow cells, whereas DNA strand break levels were not (Dobrzyńska et al., 2014). In mice, intravenous injection of silver ions or nanoparticles had no effect on emerging sperm cells with anomalous head morphology or on DNA strand breaks in spleen cells (Ordzhonikidze et al., 2009). In bone marrow cells from mice intraperitoneally injected with silver nanoparticles, there were increased chromosomal aberrations but no increase in DNA strand breaks (Ghosh et al., 2012). Mice dosed by the same route with silver iodide showed no increase in sister chromatic exchanges in P388 lymphocyte leukemia cells (Eliopoulos and Mourelatos, 1998). In rats, inhalation of silver nanoparticles induced DNA strand breaks in lung cells (Cho et al., 2013), and silver nanoparticles had no effect on micronuclei levels in bone marrow cells after oral dosing (Kim et al., 2008).

In summary, metallic silver may induce DNA strand breaks in mononuclear leukocytes. Nanoparticles increased micronuclei, DNA strand breaks, and the number of sperm cells with anomalous head morphology. However, additional data are required before firm conclusions can be drawn regarding the genotoxic potential of silver *in vivo*.

6.3. Carcinogenesis

Mice received a dermal application of a 10% silver nitrate solution twice a week for 20 weeks. 7,12-Dimethylbenz[a]anthracene (DMBA) was used as a tumorigenic inducer. There was no promotion of hyperplasia (Frei and Stephens, 1968). In a similar study design, silver nitrate was dosed twice weekly for 44 weeks. Three out of 22 mice bore a total of 8 papillomas; however, when a single application of croton oil (5%) was interspersed between DMBA and silver nitrate, 6 out of 20 mice developed a total of 14 tumors, 1 of which was a carcinoma (Saffiotti and Shubik, 1963). Rats had 1.5 cm disks of silver or tin foil embedded in their abdominal wall. Following a latent period of 275–625 days, 14 tumors (32%) were found in the silver group. No tumors were found in the tin group. The silver disks were intact, whereas the tin had broken up and crumbled into a fragmentary mass. It was discussed whether the physical nature of the disks caused the tumors and not the chemical nature of silver (Oppenheimer et al., 1956). Silver, gold, or platinum disks (1 mm^2 in area) were subcutaneously implanted in rats. No sarcomas were observed at 18 months of exposure (Nothdurft, 1958). Rats were injected with 2.5 mg colloidal silver per week for 7 months (~1.4 mg/kg bw/day). Argyria developed after 6–8 weeks, and at the end of the 7-month period, 6 out of 26 animals had tumors (spindle cell sarcomas) at the injection site (Schmãhl and Steinhoff, 1960). Rats were intramuscularly injected with so-called *300 mesh fine silver powder* (5 injections of 5 mg followed by 5 injections of 10 mg, ~600 mg/kg bw). The rats were observed for 24 months and silver was not carcinogenic. The positive control, cadmium, was carcinogenic (Furst and Schlauder, 1978).

In summary, the findings point in different directions, and additional studies on are required before a firm conclusion can be drawn regarding whether silver is carcinogenic.

7. Other toxicological endpoints

7.1. Neurotoxicity

A 59-year-old man was treated for ulcers with silver sulfadiazine at a dose of 1 mg silver/kg bw/day every second day for 5 months (cumulative dose: 160 mg silver/kg bw). Sensation loss was noted over the forearms and legs (Payne et al., 1992). A woman with generalized dystrophic epidermolysis bullosa was treated with silver sulfate cream over the course of many years (~0.1 mg silver/kg bw/day). She developed a loss of proprioception, a tingling sensation in her limbs, and impaired coordination (Flohr et al., 2008).

7.2. Hepatic toxicity

Burn patients treated with silver sulfadiazine for various time periods had elevated liver enzyme activities that correlated to serum levels of silver (Coombs et al., 1992). A 17-year-old male burn patient was treated with nanocrystalline silver dressing for one week with (~35 mg silver/kg bw/day). Liver enzymes were upregulated during exposure but normalized upon discontinuation of the dressing (Trop et al., 2006).

7.3. Renal toxicity

Following the treatment of burns with a 0.5% silver nitrate solution, argyria with depletion of body sodium chloride was observed in 1 out of 15 patients (Moyer et al., 1965). Renal dysfunction developed in a woman treated with 100 g of 1% silver sulfadiazine cream per week for 18 months (~0.6 mg/kg bw/day or a cumulative dose of ~325 mg/kg bw). The level of silver in blood was 38 µg/L. However, a female burn wound patient treated with silver sulfadiazine and having a silver blood concentration of 440 µg/L had normal renal function (Maitre et al., 2002). A burn wound developing after the spraying of a ruptured conduit that contained 60% sulfuric acid and 40% nitric acid at 60°C was treated with silver sulfadiazine for

60 days, during which nephrotic syndrome developed. Improved renal function and remission of proteinuria occurred after 5 months of therapy with immunosuppressive agents (Owens et al., 1974). A 61-year-old woman with ulcers was treated with 200 g of silver sulfadiazine cream daily for 3 weeks and developed renal failure (~180 mg silver/kg bw). The blood level of silver was 196 µg/L. The signs regressed upon withdrawal of the cream and after several sessions of hemodialysis (Chaby et al., 2005). A woman with a burn covering 70% of the total body surface area was treated with 8,000 cm^2 silver-containing silicone foam dressing for 7 days and developed kidney failure. She subsequently developed multiorgan system dysfunction and eventually died (McCague and Joe, 2015).

7.4. Hematological toxicity

There are several reports that indicate leukopenia is associated with the use of silver sulfadiazine in humans (Caffee and Bingham, 1982; Chaby et al., 2005; Chan et al., 1976; Fraser and Beaulieu, 1979; Gbaanador et al., 1987; Jarrett et al., 1978; Lockhart et al., 1983; Valente and Axelrod, 1978; Viala et al., 1997; Wilson et al., 1986). In support of this assertion, silver sulfadiazine was applied to mice with full-thickness skin excision covering 10% of the body surface, resulting in a reduction in total peripheral blood leukocyte counts (Gamelli et al., 1993). The findings of 2 controlled human studies have not supported that silver sulfadiazine induces leukopenia (Kiker et al., 1977; Thomson et al., 1989), and neutropenia sometimes occurs as an adverse effect of sulfadiazine in the absence of silver (Chen et al., 1991; Finland et al., 1984; Marshall et al., 1950; McMillin, 1951; Trepanier, 2004). However, in absence of sulfadiazine, leukopenia was reported in a burn patient treated with a silver-containing silicone foam dressing for 7 days (McCague and Joe, 2015).

Methemoglobinemia secondary to dermal silver nitrate therapy has been reported (Chou et al., 1999; Cushing and Smith, 1969; Strauch et al., 1969a, 1969b). Methemoglobinemia was also reported following the exposure to nitrate alone; thus, nitrate and not silver may be responsible for the effect (Inoue et al., 1999).

8. Comparison of ionic and nanoparticulate silver

Silver nanoparticles could be expected to act differently than silver ions: 1) they could act as a physical entity, for example, by breaking a cell wall or obstructing a vessel (only free nanoparticles); 2) they could provide a surface milieu in which chemical reactions could occur or molecules be absorbed and immobilized; or 3) they could release ions. The release of silver ions from the surface of metallic silver has been demonstrated *in vivo* (Danscher and Locht, 2010). The studies described in the present review that compare silver ions with nanoparticles and nanocrystalline coatings use animals and indicate a similar effect of silver ions and nanoformulated silver (Guo et al., 2016; Korani et al., 2013; Li et al., 2016; Nadworny et al., 2010; Ordzhonikidze et al., 2009; Pfurtscheller et al., 2014); and this is also observed to be the case for oral exposure to silver (Hadrup et al., 2012; Hadrup and Lam, 2014). One dermal exception is a study in which skin irritation was observed with silver nanoparticles but not silver nitrate (Koohi, M K; Hejazy, M; Asadi, F; Asadian, 2011).

9. Risk characterization

The question is, what are the critical effects of dermal and mucosal silver? The 7 g dosage of intrauterine silver nitrate as an abortion procedure caused mortality. This dose corresponds to 64 mg silver/kg bw. In guinea pigs, 130 mg silver/kg bw given as a skin depot caused weight loss. Regarding generalized argyria, this has been reported in humans with estimated cumulative doses as low as 70 mg/kg bw (Lee and Lee, 1994). Collectively, these findings suggest that critical effects start to occur at cumulative doses in the range of 60 to 70 mg silver/kg bw. Regarding the ultimate endpoint of genotoxicity and carcinogenicity, the evidence is conflicting as to the role of silver; although most have been negative, more studies on the carcinogenic potential would be relevant.

10. Summary

By the dermal and mucosal surface exposure route, intact skin is observed to be an effective barrier; however, silver is taken up through the mucosal surfaces and compromised skin. Deposition occurs in a range of organs and involves deposition as particles in the form of silver combined with other elements, including sulfur and selenium. The deposition of silver as particles causes discoloration known as argyria. Excretion after exposure by the dermal and mucosal surface routes involves increased levels in urine and feces. The elimination from plasma is prolonged, lasting several of hundreds of days.

Regarding toxicity, a case of mortality was observed at intrauterine exposure to ionic silver at 64 mg/kg bw. Localized argyria has been reported with exposure to silver ions, metallic surfaces, and nanocrystalline silver. Generalized argyria was observed with ionic and nanocrystalline silver in humans at cumulative doses in the range of 70 to 1500 mg silver/kg body weight. Silver is observed to have a low potential for skin irritation. Eye irritation and some cases of allergic contact dermatitis have been reported. Silver may cause genotoxicity, but additional data are required to assess its carcinogenic potential. Other reported toxicities include hepatic, renal, neurological, and hematological effects.

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Conflicts of interest

The authors declare there are no conflicts of interest.

References

Agarwal, S., Gawkrodger, D.J., 2002. Occupational allergic contact dermatitis to silver and colophonium in a jeweler. Am. J. Contact Dermat. 13, 74.

Aktepe, N., Kocyigit, A., Yukselten, Y., Taskin, A., Keskin, C., Celik, H., 2015. Increased DNA damage and oxidative stress among silver jewelry workers. Biol. Trace Elem. Res. 164, 185–91. doi:10.1007/s12011-014-0224-0

Asare, N., Instanes, C., Sandberg, W.J., Refsnes, M., Schwarze, P., Kruszewski, M., Brunborg, G., 2012. Cytotoxic and genotoxic effects of silver nanoparticles in testicular cells. Toxicology 291, 65–72. doi:10.1016/j.tox.2011.10.022

AshaRani, P. V, Low Kah, M.G., Hande, M.P., Valiyaveettil, S., 2009. Cytotoxicity and genotoxicity of silver nanoparticles in human cells. ACS Nano. 3, 279–290.

Bader, K.F., 1966. Organ deposition of silver following silver nitrate therapy of burns. Plast. Reconstr. Surg. 37, 550–1.

Bartley, G.B., 1991. Pigmented Episcleral Mass From Argyrosis Following Strabismus Surgery. Arch. Ophthalmol. 109, 775. doi:10.1001/archopht.1991.01080060031013

Berry, J.P., Galle, P., 1982. Selenium and kidney deposits in experimental argyria. Electron microscopy and microanalysis. Pathol. Biol. (Paris). 30, 136–40.

Berry, J.P., Zhang, L., Galle, P., 1995. Interaction of selenium with copper, silver, and gold salts. Electron microprobe study. J. Submicrosc. Cytol. Pathol. 27, 21–8.

Bianco, C., Visser, M.J., Pluut, O.A., Svetličić, V., Pletikapić, G., Jakasa, I., Riethmuller, C., Adami, G., Larese Filon, F., Schwegler-Berry, D., Stefaniak, A.B., Kezic, S., 2016. Characterization of silver particles in the stratum corneum of healthy subjects and atopic dermatitis patients dermally exposed to a silver-containing garment. Nanotoxicology 10, 1480–1491. doi:10.1080/17435390.2016.1235739

Bleehen, S.S., Gould, D.J., Harrington, C.I., Durrant, T.E., Slater, D.N., Underwood, J.C., 1981. Occupational argyria; light and electron microscopic studies and X-ray microanalysis. Br. J. Dermatol. 104, 19–26.

Boosalis, M.G., McCall, J.T., Ahrenholz, D.H., Solem, L.D., McClain, C.J., 1987. Serum and urinary silver levels in thermal injury patients. Surgery 101, 40–3.

Bouterie, R.L., McLean, D.H., 1971. Use of 0.5 per cent silver nitrate cream for burns. Am. J. Surg. 121, 576–9.

Brouillard, C., Bursztejn, A.-C., Latarche, C., Cuny, J.-F., Truchetet, F., Goullé, J.-P., Schmutz, J.-L., 2018. Silver absorption and toxicity evaluation of silver wound dressings in 40 patients with chronic wounds. J. Eur. Acad. Dermatol. Venereol. doi:10.1111/jdv.15055

Browning, J.C., Levy, M.L., 2008. Argyria attributed to silvadene application in a patient with dystrophic epidermolysis bullosa. Dermatol. Online J. 14, 9.

Buckley, W.R., Oster, C.F., Fassett, D.W., 1965. Localized Argyria - II Chemical Nature of Silver Containing Particles. Arch. Dermatol. 92, 697. doi:10.1001/archderm.1965.01600180089018

Caffee, H.H., Bingham, H.G., 1982. Leukopenia and silver sulfadiazine. J. Trauma 22, 586–7.

Calvery, H.O., 1941. EFFECTS OF SOME SILVER SALTS ON THE EYE. Arch. Ophthalmol. 25, 839. doi:10.1001/archopht.1941.00870110091010

CAS, 2018. SciFinder [WWW Document]. URL https://www.cas.org/products/scifinder

Catsakis, L.H., Sulica, V.I., 1978. Allergy to silver amalgams. Oral Surg. Oral Med. Oral Pathol. 46, 371–5.

Chaby, G., Viseux, V., Poulain, J.-F., De Cagny, B., Denoeux, J.-P., Lok, C., 2005. [Topical silver sulfadiazine-induced acute renal failure]. Ann. dermatologie vénéréologie 132, 891–3.

Chan, C.K., Jarrett, F., Moylan, J.A., 1976. Acute leukopenia as an allergic reaction to silver sulfadiazine in burn patients. J. Trauma 16, 395–6.

Chen, Z., Peto, R., Collins, R., MacMahon, S., Lu, J., Li, W., 1991. Serum cholesterol concentration and coronary heart disease in population with low cholesterol concentrations. BMJ 303, 276–282.

Cho, H., Sung, J., Song, K., Kim, J., Ji, J., Lee, J., Ryu, H., Ahn, K., Yu, I., 2013. Genotoxicity of Silver Nanoparticles in Lung Cells of Sprague Dawley Rats after 12 Weeks of Inhalation Exposure. Toxics 1, 36–45. doi:10.3390/toxics1010036

Chou, T.D., Gibran, N.S., Urdahl, K., Lin, E.Y., Heimbach, D.M., Engrav, L.H., 1999. Methemoglobinemia secondary to topical silver nitrate therapy--a case report. Burns 25, 549–52.

Clemente, G.F., Cignarossi, L., Santaroni, G.P., 1977. Trace element intake and excretion in the italian population. J. Radioanal. Chem. 37, 549–558.

Coombs, C.J., Wan, A.T., Masterton, J.P., Conyers, R.A., Pedersen, J., Chia, Y.T., 1992. Do burn patients have a silver lining? Burns 18, 179–84.

Cushing, A.H., Smith, S., 1969. Methemoglobinemia with silver nitrate therapy of a burn; report of a case. J. Pediatr. 74, 613–5.

Danscher, G., Locht, L.J., 2010. In vivo liberation of silver ions from metallic silver surfaces. Histochem. Cell Biol. 133, 359–66. doi:10.1007/s00418-009-0670-5

Dobrzyńska, M.M., Gajowik, A., Radzikowska, J., Lankoff, A., Dušinská, M., Kruszewski, M., 2014. Genotoxicity of silver and titanium dioxide nanoparticles in bone marrow cells of rats in vivo. Toxicology 315, 86–91. doi:10.1016/j.tox.2013.11.012

Dunn, K., Edwards-Jones, V., 2004. The role of Acticoat with nanocrystalline silver in the management of burns. Burns 30 Suppl 1, S1-9.

Eliopoulos, P., Mourelatos, D., 1998. Lack of genotoxicity of silver iodide in the SCE assay in vitro, in vivo, and in the Ames/microsome test. Teratog. Carcinog. Mutagen. 18, 303–308.

Eom, H.J., Choi, J., 2010. p38 MAPK activation, DNA damage, cell cycle arrest and apoptosis as mechanisms of toxicity of silver nanoparticles in Jurkat T cells. Environ.Sci.Technol. 44, 8337–8342.

FDA, 2017. Strength Conversion in Drug Listing.

Ferrara, G., Filosa, A., Mariani, M.P., Fasanella, L., 2018. Occupational Argyria of the Nasal Mucosa. Head Neck Pathol. 12, 252–254. doi:10.1007/s12105-017-0842-x

Finland, M., Strauss, E., Peterson, O.L., 1984. Landmark article June 14, 1941: Sulfadiazine. Therapeutic evaluation and toxic effects on four hundred and forty-six patients. By Maxwell Finland, Elias Strauss, and Osler L. Peterson. JAMA 251, 1467–74.

Fisher, N.M., Marsh, E., Lazova, R., 2003. Scar-localized argyria secondary to silver sulfadiazine cream. J. Am. Acad. Dermatol. 49, 730–2.

Flohr, C., Heague, J., Leach, I., English, J., 2008. Topical silver sulfadiazine-induced systemic argyria in a patient with severe generalized dystrophic epidermolysis bullosa. Br. J. Dermatol. 159, 740–1. doi:10.1111/j.1365-2133.2008.08690.x

Fluhr, J.W., Breternitz, M., Kowatzki, D., Bauer, A., Bossert, J., Elsner, P., Hipler, U.-C., 2010. Silver-loaded seaweed-based cellulosic fiber improves epidermal skin physiology in atopic dermatitis: safety assessment, mode of action and controlled, randomized single-blinded exploratory in vivo study. Exp. Dermatol. 19, e9-15. doi:10.1111/j.1600-0625.2009.00943.x

Fox, C.L., 1975. Silver sulfadiazine for control of burn wound infections. Int. Surg. 60, 275–7.

Fraser-Moodie, A., 1992. Sensitivity to silver in a patient treated with silver sulphadiazine (Flamazine). Burns 18, 74–5.

Fraser, G.L., Beaulieu, J.T., 1979. Leukopenia secondary to sulfadiazine silver. JAMA 241, 1928–9.

Frei, J. V, Stephens, P., 1968. The correlation of promotion of tumour growth and of induction of hyperplasia in epidermal two-stage carcinogenesis. Br. J. Cancer 22, 83–92.

Furst, A., Schlauder, M.C., 1978. Inactivity of two noble metals as carcinogens. J. Environ. Pathol. Toxicol. 1, 51–7.

Gamelli, R.L., Paxton, T.P., O'Reilly, M., 1993. Bone marrow toxicity by silver sulfadiazine. Surg. Gynecol. Obstet. 177, 115–20.

García-Martínez, P., López Aventín, D., Segura, S., Gómez-Martín, I., Lloreta, J., Ibáñez, J., Elvira, J.J., Pujol, R.M., 2016. In vivo reflectance confocal microscopy characterization of silver deposits in localized cutaneous argyria. Br. J. Dermatol. 175, 1052–1055. doi:10.1111/bjd.14571

Gaul, L.E., 1954. Incidence of sensitivity to chromium, nickel, gold, silver and copper compared to reactions to their aqueous salts including cobalt sulfate. Ann. Allergy 12, 429–44.

Gbaanador, G.B., Policastro, A.J., Durfee, D., Bleicher, J.N., 1987. Transient leukopenia associated with topical silver sulfadiazine in burn therapy. Nebr. Med. J. 72, 83–5.

Gee Kee, E., Kimble, R.M., Cuttle, L., Stockton, K., 2013. Comparison of three different dressings for partial thickness burns in children: study protocol for a randomised controlled trial. Trials 14, 403. doi:10.1186/1745-6215-14-403

Genuino, G.A.S., Baluyut-Angeles, K.V., Espiritu, A.P.T., Lapitan, M.C.M., Buckley, B.S., 2014. Topical petrolatum gel alone versus topical silver sulfadiazine with standard gauze dressings for the treatment of superficial partial thickness burns in adults: a randomized controlled trial. Burns 40, 1267–73. doi:10.1016/j.burns.2014.07.024

Gherardi, R., Brochard, P., Chamak, B., Bernaudin, J.F., Duckett, S., Poirier, J., 1984. Human generalized argyria. Arch. Pathol. Lab. Med. 108, 181–2.

Ghosh, M., J, M., Sinha, S., Chakraborty, A., Mallick, S.K., Bandyopadhyay, M., Mukherjee, A., 2012. In vitro and in vivo genotoxicity of silver nanoparticles. Mutat. Res. 749, 60–9. doi:10.1016/j.mrgentox.2012.08.007

Gibson, R.S., Scythes, C.A., 1984. Chromium, selenium, and other trace element intakes of a selected sample of Canadian premenopausal women. Biol. Trace Elem. Res. 6, 105–16. doi:10.1007/BF02916928

Goff, H., Powers, E.L., 1975. Effects of X-rays on Ag-DNA Complexes. Int. J. Radiat. Biol. Relat. Stud. Physics, Chem. Med. 27, 503–507. doi:10.1080/09553007514550511

Griffiths, M.R., Milne, J.T., Porter, W.M., 2006. Penile argyria. Br. J. Dermatol. 155, 1074–1075. doi:10.1111/j.1365-2133.2006.07463.x

Guo, X., Li, Y., Yan, J., Ingle, T., Jones, M.Y., Mei, N., Boudreau, M.D., Cunningham, C.K., Abbas, M., Paredes, A.M., Zhou, T., Moore, M.M., Howard, P.C., Chen, T., 2016. Size- and coating-dependent cytotoxicity and genotoxicity of silver nanoparticles evaluated using in vitro standard assays. Nanotoxicology 10, 1373–1384. doi:10.1080/17435390.2016.1214764

Hackenberg, S., Scherzed, A., Kessler, M., Hummel, S., Technau, A., Froelich, K., Ginzkey, C., Koehler, C., Hagen, R., Kleinsasser, N., 2011. Silver nanoparticles: evaluation of DNA damage, toxicity and functional impairment in human mesenchymal stem cells. Toxicol. Lett. 201, 27–33. doi:10.1016/j.toxlet.2010.12.001

Hadrup, N., Lam, H.R., 2014. Oral toxicity of silver ions, silver nanoparticles and colloidal silver--a review. Regul. Toxicol. Pharmacol. 68, 1–7. doi:10.1016/j.yrtph.2013.11.002

Hadrup, N., Loeschner, K., Mortensen, A., Sharma, A.K., Qvortrup, K., Larsen, E.H., Lam, H.R., 2012. The similar neurotoxic effects of nanoparticulate and ionic silver in vivo and in vitro. Neurotoxicology 33, 416–423.

Hamilton, E.I., Minski, M.J., Cleary, J.J., 1973. The concentration and distribution of some stable elements in healthy human tissues from the United Kingdom An environmental study. Sci. Total Environ. 1, 341–374. doi:10.1016/0048-9697(73)90024-7

Hau, S.C., Tuft, S.J., 2009. Presumed corneal argyrosis from occlusive soft contact lenses: a case report. Cornea 28, 703–5. doi:10.1097/ICO.0b013e31818f9724

Heyl, T., 1979. Contact dermatitis from silver coat. Contact Dermatitis 5, 197.

Hipler, U.-C., Elsner, P., Fluhr, J.W., 2006. A new silver-loaded cellulosic fiber with antifungal and antibacterial properties. Curr. Probl. Dermatol. 33, 165–78. doi:10.1159/000093944

Hollander, L., 1955. Dermatitis caused by metal strands. AMA. Arch. Derm. 71, 735.

Hristov, A.C., High, W.A., Golitz, L.E., 2011. Localized cutaneous argyria. J. Am. Acad. Dermatol. 65, 660–661. doi:10.1016/j.jaad.2010.05.016

Inoue, T., Terris, J., Ecelbarger, C.A., Chou, C.L., Nielsen, S., Knepper, M.A., 1999. Vasopressin regulates apical targeting of aquaporin-2 but not of UT1 urea transporter in renal collecting duct. Am.J.Physiol 276, F559–F566.

Jankićević, J., Vesić, S., Vukićević, J., Gajić, M., Adamic, M., Pavlović, M.D., 2008. Contact sensitivity in patients with venous leg ulcers in Serbia: comparison with contact dermatitis patients and relationship to ulcer duration. Contact Dermatitis 58, 32–6. doi:10.1111/j.1600-0536.2007.01253.x

Jarrett, F., Ellerbe, S., Demling, R., 1978. Acute leukopenia during topical burn therapy with silver sulfadiazine. Am. J. Surg. 135, 818–9.

Kakurai, M., Demitsu, T., Umemoto, N., Ohtsuki, M., Nakagawa, H., 2003. Activation of mast cells by silver particles in a patient with localized argyria due to implantation of acupuncture needles. Br. J. Dermatol. 148, 822.

Kamiya, K., Yamasaki, O., Tachikawa, S., Iwatsuki, K., 2011. Localized cutaneous argyria in a silversmith. Eur. J. Dermatol. 23, 6–9. doi:10.1684/ejd.2012.1892

Kapur, N., Landon, G., Yu, R.C., 2001. Localized argyria in an antique restorer. Br. J. Dermatol. 144, 191–193. doi:10.1046/j.1365-2133.2001.03977.x

Karcioglu, Z.A., Caldwell, D.R., 1985. Corneal argyrosis: histologic, ultrastructural and microanalytic study. Can. J. Ophthalmol. 20, 257–60.

Kermanizadeh, A., Vranic, S., Boland, S., Moreau, K., Baeza-Squiban, A., Gaiser, B.K., Andrzejczuk, L.A., Stone, V., 2013. An in vitro assessment of panel of engineered nanomaterials using a human renal cell line: cytotoxicity, pro-inflammatory response, oxidative stress and genotoxicity. BMC Nephrol. 14, 96. doi:10.1186/1471-2369-14-96

Kiker, R.G., Carvajal, H.F., Mlcak, R.P., Larson, D.L., 1977. A controlled study of the effects of silver sulfadiazine on white blood cell counts in burned children. J. Trauma 17, 835–6.

Kim, H.R., Park, Y.J., Shin, D.Y., Oh, S.M., Chung, K.H., 2013. Appropriate in vitro methods for genotoxicity testing of silver nanoparticles. Environ. Health Toxicol. 28, e2013003. doi:10.5620/eht.2013.28.e2013003

Kim, J.S., Song, K.S., Sung, J.H., Ryu, H.R., Choi, B.G., Cho, H.S., Lee, J.K., Yu, I.J., 2013. Genotoxicity, acute oral and dermal toxicity, eye and dermal irritation and corrosion and skin sensitisation evaluation of silver nanoparticles. Nanotoxicology 7, 953–60. doi:10.3109/17435390.2012.676099

Kim, Y.S., Kim, J.S., Cho, H.S., Rha, D.S., Kim, J.M., Park, J.D., Choi, B.S., Lim, R., Chang, H.K., Chung, Y.H., Kwon, I.H., Jeong, J., Han, B.S., Yu, I.J., 2008. Twenty-Eight-Day Oral Toxicity, Genotoxicity, and Gender-Related Tissue Distribution of Silver Nanoparticles in Sprague-Dawley Rats. Inhal. Toxicol. 20, 575–583. doi:10.1080/08958370701874663

Kleckner Jr., M.S., 1949. The use of BAL in generalized argyria. Calif. Med. 70, 133.

Koohi, M K; Hejazy, M; Asadi, F; Asadian, P., 2011. Assessment of dermal exposure and histopathologic changes of different sized nano-silver in healthy adult rabbits. J. ofPhysicsConference Ser. 304, 1–9.

Korani, M., Rezayat, S.M., Arbabi Bidgoli, S., 2013. Sub-chronic Dermal Toxicity of Silver Nanoparticles in Guinea Pig: Special Emphasis to Heart, Bone and Kidney Toxicities. Iran. J. Pharm. Res. IJPR 12, 511–9.

Kruszewski, M., Grądzka, I., Bartłomiejczyk, T., Chwastowska, J., Sommer, S., Grzelak, A., Zuberek, M., Lankoff, A., Dusinska, M., Wojewódzka, M., 2013. Oxidative DNA damage corresponds to the long term survival of human cells treated with silver nanoparticles. Toxicol. Lett. 219, 151–9. doi:10.1016/j.toxlet.2013.03.006

Laine, J., Kalimo, K., Happonen, R.P., 1997. Contact allergy to dental restorative materials in patients with oral lichenoid lesions. Contact Dermatitis 36, 141–6.

Lancaster, W.B., 1920. Argyrol. Trans. Am. Ophthalmol. Soc. 18, 151–62.

Landsiedel, R., Kapp, M.D., Schulz, M., Wiench, K., Oesch, F., 2009. Genotoxicity investigations on nanomaterials: methods, preparation and characterization of test material, potential artifacts and limitations--many questions, some answers. Mutat. Res. 681, 241–58. doi:10.1016/j.mrrev.2008.10.002

Lansdown, A.B., 2006. Silver in health care: antimicrobial effects and safety in use. Curr. Probl. Dermatol. 33, 17–34. doi:10.1159/000093928

Lazare, R., Watson, P.A., Winter, G.D., 1974. Distribution and excretion of silver sulphadiazine applied to scalds in the pig. Burns 1, 57–64.

Lee, S.M., Lee, S.H., 1994. Generalized argyria after habitual use of AgNO3. J. Dermatol. 21, 50–3.

Li, Y., Chen, D.H., Yan, J., Chen, Y., Mittelstaedt, R.A., Zhang, Y., Biris, A.S., Heflich, R.H., Chen, T., 2012. Genotoxicity of silver nanoparticles evaluated using the Ames test and in vitro micronucleus assay. Mutat. Res. 745, 4–10. doi:10.1016/j.mrgentox.2011.11.010

Li, Y., Qin, T., Ingle, T., Yan, J., He, W., Yin, J.-J., Chen, T., 2016. Differential genotoxicity mechanisms of silver nanoparticles and silver ions. Arch. Toxicol. doi:10.1007/s00204-016-1730-y

Liu, J.Y., Sonshine, D.A., Shervani, S., Hurt, R.H., 2010. Controlled Release of Biologically Active Silver from Nanosilver Surfaces. ACS Nano 4, 6903–6913. doi:Doi 10.1021/Nn102272n

Lockhart, S.P., Rushworth, A., Azmy, A.A., Raine, P.A., 1983. Topical silver sulphadiazine: side effects and urinary excretion. Burns. Incl. Therm. Inj. 10, 9–12.

Loeffler, K.U., Lee, W.R., 1987. Argyrosis of the lacrimal sac. Graefe's Arch. Clin. Exp. Ophthalmol. = Albr. von Graefes Arch. für Klin. und Exp. Ophthalmol. 225, 146–50.

Luk, K.F., Maki, A.H., Hoover, R.J., 1975. Letter: Studies of heavy metal binding with polynucleotides using optical detection of magnetic resonance. Silver(I) binding. J. Am. Chem. Soc. 97, 1241–2.

Maitre, S., Jaber, K., Perrot, J.L., Guy, C., Cambazard, F., 2002. [Increased serum and urinary levels of silver during treatment with topical silver sulfadiazine]. Ann. dermatologie vénéréologie 129, 217–9.

Maneewattanapinyo, P., Banlunara, W., Thammacharoen, C., Ekgasit, S., Kaewamatawong, T., 2011. An evaluation of acute toxicity of colloidal silver nanoparticles. J. Vet. Med. Sci. 73, 1417–1423. doi:10.1292/jvms.11-0038

Marshall, C.R., Neave, E.F., 1906. THE BACTERICIDAL ACTION OF COMPOUNDS OF SILVER. Br. Med. J. 2, 359–63.

Marshall, J.P., Schneider, R.P., 1977. Systemic argyria secondary to topical silver nitrate. Arch. Dermatol. 113, 1077–9.

Marshall, M., McNamara, T.M., Schulte, J.W., 1950. Fatal acute agranulocytosis following prolonged administration of small doses of sulfadiazine for urinary bacteriostasis. Calif. Med. 72, 390–1.

Massi, D., Santucci, M., 1998. Human generalized argyria: a submicroscopic and X-ray spectroscopic study. Ultrastruct. Pathol. 22, 47–53.

Matsumura, T., Kumakiri, M., Ohkawara, A., Himeno, H., Numata, T., Adachi, R., 1992. Detection of selenium in generalized and localized argyria: report of four cases with X-ray microanalysis. J. Dermatol. 19, 87–93.

McCague, A., Joe, V.C., 2015. A Case of Argyria and Acute Leukopenia Associated with the Use of an Antimicrobial Soft Silicone Foam Dressing. J. Burn Care Res. doi:10.1097/BCR.0000000000000275

McKenna, S.R., Latenser, B.A., Jones, L.M., Barrette, R.R., Sherman, H.F., Varcelotti, J.R., 1995. Serious silver sulphadiazine and mafenide acetate dermatitis. Burns 21, 310–2.

McMillin, J.S., 1951. SUCCESSFUL USE OF ACTH IN THE TREATMENT OF AGRANULOCYTOSIS DUE TO SULFADIAZINE. Am. J. Med. Sci. 222, 392–395. doi:10.1097/00000441-195110000-00004

Mei, N., Zhang, Y., Chen, Y., Guo, X., Ding, W., Ali, S.F., Biris, A.S., Rice, P., Moore, M.M., Chen, T., 2012. Silver nanoparticle-induced mutations and oxidative stress in mouse lymphoma cells. Environ. Mol. Mutagen. 53, 409–19. doi:10.1002/em.21698

Miller, C.N., Newall, N., Kapp, S.E., Lewin, G., Karimi, L., Carville, K., Gliddon, T., Santamaria, N.M., 2010. A randomized-controlled trial comparing cadexomer iodine and nanocrystalline silver on the healing of leg ulcers. Wound Repair Regen. 18, 359–67. doi:10.1111/j.1524-475X.2010.00603.x

Moiemen, N.S., Shale, E., Drysdale, K.J., Smith, G., Wilson, Y.T., Papini, R., 2011. Acticoat dressings and major burns: systemic silver absorption. Burns 37, 27–35. doi:10.1016/j.burns.2010.09.006

Moore, D.L., MacDonald, N.E., Canadian Paediatric Society, I.D. and I.C., 2015. Preventing ophthalmia neonatorum. Paediatr. Child Health 20, 93–6.

Morton, C.A., Fallowfield, M., Kemmett, D., 1996. Localized argyria caused by silver earrings. Br. J. Dermatol. 135, 484–5.

Moyer, C.A., Brentano, L., Gravens, D.L., Margraf, H.W., Monafo, W.W., 1965. TREATMENT OF LARGE HUMAN BURNS WITH 0.5 PER CENT SILVER NITRATE SOLUTION. Arch. Surg. 90, 812–67.

Nadworny, P.L., Landry, B.K., Wang, J., Tredget, E.E., Burrell, R.E., 2010. Does nanocrystalline silver have a transferable effect? Wound Repair Regen. 18, 254–65. doi:10.1111/j.1524-475X.2010.00579.x

Nagano, T., Oka, M., Horikawa, T., Nishigori, C., Kotera, M., 2016. Single, blue nevus-like localized argyria. J. Dermatol. 43, 1359–1360. doi:10.1111/1346-8138.13387

Nakane, T., Gomyo, H., Sasaki, I., Kimoto, Y., Hanzawa, N., Teshima, Y., Namba, T., 2006. New antiaxillary odour deodorant made with antimicrobial Ag-zeolite (silver-exchanged zeolite). Int. J. Cosmet. Sci. 28, 299–309. doi:10.1111/j.1467-2494.2006.00322.x

Nothdurft, H., 1958. �ber die Nichtexistenz von ?Metallkrebs? im Falle der Edelmetalle. Naturwissenschaften 45, 549–550. doi:10.1007/BF00632073

Oppenheimer, B.S., Oppenheimer, E.T., Danishefsky, I., Stout, A.P., 1956. Carcinogenic effect of metals in rodents. Cancer Res. 16, 439–41.

Ordzhonikidze, C.G., Ramaiyya, L.K., Egorova, E.M., Rubanovich, A. V, 2009. Genotoxic Effects of Silver Nanoparticles on Mice in Vivo . Acta Naturae 1, 99–101.

Owens, C.J., Yarbrough, D.R., Brackett, N.C., 1974. Nephrotic syndrome following topically applied sulfadiazine silver therapy. Arch. Intern. Med. 134, 332–5.

Ozkaya, E., 2009. A rare case of allergic contact dermatitis from silver nitrate in a widely used special patch test marker. Contact Dermatitis 61, 120–2. doi:10.1111/j.1600-0536.2009.01566.x

Palamar, M., 2010. Black Tears (Melanodacryorrhea) From Argyrosis. Arch. Ophthalmol. 128, 503. doi:10.1001/archophthalmol.2010.37

Pariser, R.J., 1978. Generalized argyria. Clinicopathologic features and histochemical studies. Arch. Dermatol. 114, 373–7.

Park, M.V.D.Z., Neigh, A.M., Vermeulen, J.P., de la Fonteyne, L.J.J., Verharen, H.W., Briedé, J.J., van Loveren, H., de Jong, W.H., 2011. The effect of particle size on the cytotoxicity, inflammation, developmental toxicity and genotoxicity of silver nanoparticles. Biomaterials 32, 9810–9817. doi:10.1016/j.biomaterials.2011.08.085

Park, M.Y., Lee, J.S., Jin, H.J., You, H.S., Kim, G.W., Ko, H.C., Kim, B.S., Kim, M.B., Kim, H.S., 2018. Localized argyria: troublesome side-effect of acupuncture. J. Eur. Acad. Dermatol. Venereol. 32, e62–e65. doi:10.1111/jdv.14526

Payne, C.M., Bladin, C., Colchester, A.C., Bland, J., Lapworth, R., Lane, D., 1992. Argyria from excessive use of topical silver sulphadiazine. Lancet (London, England) 340, 126.

Pfizer, 2016. SILVADENE- silver sulfadiazine cream [WWW Document]. URL http://labeling.pfizer.com/ShowLabeling.aspx?id=701

Pfurtscheller, K., Petnehazy, T., Goessler, W., Bubalo, V., Kamolz, L.-P., Trop, M., 2014. Transdermal uptake and organ distribution of silver from two different wound dressings in rats after a burn trauma. Wound Repair Regen. 22, 654–9. doi:10.1111/wrr.12209

Polk, H.C., 1966. Treatment of severe burns with aqueous silver nitrate (0.5 percent). Ann. Surg. 164, 753–70.

Pubmed, 2018. Pubmed [WWW Document]. URL www.pubmed.com

Reinhardt, G., Geldmacher-von Mallinck, Kittel, H., Opitz, O., 1971. [Acute fatal poisoning with silver nitrate following an abortion attempt]. Arch. für Kriminologie 148, 69–78.

Rich, L.L., Epinette, W.W., Nasser, W.K., 1972. Argyria Presenting as Cyanotic Heart-Disease. Am. J. Cardiol. 30, 290-. doi:Doi 10.1016/0002-9149(72)90075-6

Robinson-Bostom, L., Pomerantz, D., Wilkel, C., Mader, R., Lerner, L., Dufresne, R., Flotte, T., 2002. Localized argyria with pseudo-ochronosis. J. Am. Acad. Dermatol. 46, 222–7.

Rongioletti, F., Robert, E., Buffa, P., Bertagno, R., Rebora, A., 1992. Blue nevi-like dotted occupational argyria. J. Am. Acad. Dermatol. 27, 1015–6.

Rosenblatt, M.J., Cymet, T.C., 1987. Argyria: report of a case associated with abnormal electroencephalographic and brain scan findings. J. Am. Osteopath. Assoc. 87, 509–12.

Rungby, J., 1986. The silver nitrate prophylaxis of Credé causes silver deposition in the cornea of experimental animals. Exp. Eye Res. 42, 93–4.

Sabbioni, E., Girardi, F., 1977. Metallobiochemistry of heavy metal pollution: nuclear and radiochemical techniques for long term--low level exposure (LLE) experiments. Sci. Total Environ. 7, 145–79.

Saffiotti, U., Shubik, P., 1963. Studies on promoting action in skin carcinogenesis. Natl. Cancer Inst. Monogr 10.

Samberg, M.E., Oldenburg, S.J., Monteiro-Riviere, N.A., 2010. Evaluation of silver nanoparticle toxicity in skin in vivo and keratinocytes in vitro. Environ. Health Perspect. 118, 407–13. doi:10.1289/ehp.0901398

Sano, S., Fujimori, R., Takashima, M., Itokawa, Y., 1982. Absorption, excretion and tissue distribution of silver sulphadiazine. Burns. Incl. Therm. Inj. 8, 278–85.

Sato, S., Sueki, H., Nishijima, A., 1999. Two unusual cases of argyria: the application of an improved tissue processing method for X-ray microanalysis of selenium and sulphur in silver-laden granules. Br. J. Dermatol. 140, 158–63.

Schlötzer-Schrehardt, U., Holbach, L.M., Hofmann-Rummelt, C., Naumann, G.O., 2001. Multifocal corneal argyrosis after an explosion injury. Cornea 20, 553–7.

Schmãhl, D., Steinhoff, D., 1960. Versuche zur Krebserzeugung mit kolloidalen Silber und Goldlõsungen an Ratten. Z. Krebsforsch. 63, 586–591.

Schröder, B., Nickel, U., Meyer, E., Lee, G., 2012. Transdermal delivery using a novel electrochemical device, part 2: in vivo study in humans. J. Pharm. Sci. 101, 2262–8. doi:10.1002/jps.23108

Shall, L., Stevens, A., Millard, L.G., 1990. An unusual case of acquired localized argyria. Br. J. Dermatol. 123, 403–7.

Shaub, A.R., Brown, P.J., Kobayashi, T.T., Lewin-Smith, M.R., Lupton, G.P., Hivnor, C.M., 2014. Dystrophic Calcification and Accentuated Localized Argyria After Fractionated Carbon Dioxide Laser Therapy of Hypertrophic Scars. JAMA Dermatology 150, 312. doi:10.1001/jamadermatol.2013.8044

Smith_&_Nephew_Healthcare_Ltd, 2011. FLAMAZINE Cream 1 % w/w [WWW Document]. URL https://www.smith-nephew.com/global/assets/pdf/products/wound/v1-api-flamazine-ireland-aug-2011.pdf

Souza, T.A.J., Franchi, L.P., Rosa, L.R., da Veiga, M.A.M.S., Takahashi, C.S., 2016. Cytotoxicity and genotoxicity of silver nanoparticles of different sizes in CHO-K1 and CHO-XRS5 cell lines. Mutat. Res. Genet. Toxicol. Environ. Mutagen. 795, 70–83. doi:10.1016/j.mrgentox.2015.11.002

Stefaniak, A.B., Duling, M.G., Lawrence, R.B., Thomas, T.A., LeBouf, R.F., Wade, E.E., Virji, M.A., 2014. Dermal exposure potential from textiles that contain silver nanoparticles. Int. J. Occup. Environ. Health 20, 220–34. doi:10.1179/2049396714Y.0000000070

Strauch, B., Buch, W., Grey, W., Laub, D., 1969a. Successful treatment of methemoglobinemia secondary to silver nitrate therapy. N. Engl. J. Med. 281, 257–8. doi:10.1056/NEJM196907312810509

Strauch, B., Buch, W., Grey, W., Laub, D., 1969b. Methemoglobinemia: a complication of silver nitrite therapy used in burns. AORN J. 10, 54–6.

Sugden, P., Azad, S., Erdmann, M., 2001. Argyria caused by an earring. Br. J. Plast. Surg. 54, 252–3. doi:10.1054/bjps.2000.3543

Suzuki, H., Baba, S., Uchigasaki, S., Murase, M., 1993. Localized argyria with chrysiasis caused by implanted acupuncture needles. Distribution and chemical forms of silver and gold in cutaneous tissue by electron microscopy and x-ray microanalysis. J. Am. Acad. Dermatol. 29, 833–7.

Tanita, Y., Kato, T., Hanada, K., Tagami, H., 1985. Blue macules of localized argyria caused by implanted acupuncture needles. Electron microscopy and roentgenographic microanalysis of deposited metal. Arch. Dermatol. 121, 1550–2.

Tendler, I., Pulitzer, M.P., Roggli, V., Abramson, D.H., Marr, B.P., 2017. Ocular Argyrosis Mimicking Conjunctival Melanoma. Cornea 36, 747–748. doi:10.1097/ICO.0000000000001191

Thomson, P.D., Moore, N.P., Rice, T.L., Prasad, J.K., 1989. Leukopenia in acute thermal injury: evidence against topical silver sulfadiazine as the causative agent. J. Burn Care Rehabil. 10, 418–20.

Tomi, N.S., Kränke, B., Aberer, W., 2004. A silver man. Lancet (London, England) 363, 532. doi:10.1016/S0140-6736(04)15540-2

Trepanier, L.A., 2004. Idiosyncratic toxicity associated with potentiated sulfonamides in the dog. J. Vet. Pharmacol. Ther. 27, 129–38. doi:10.1111/j.1365-2885.2004.00576.x

Trop, M., Novak, M., Rodl, S., Hellbom, B., Kroell, W., Goessler, W., 2006. Silver-coated dressing acticoat caused raised liver enzymes and argyria-like symptoms in burn patient. J. Trauma 60, 648–52. doi:10.1097/01.ta.0000208126.22089.b6

Utikal, J., Thoelke, A., Becker, J.C., Figl, R., Goerdt, S., Schadendorf, D., Ugurel, S., 2006. Local cutaneous argyria mimicking melanoma metastases in a patient with disseminated melanoma. J. Am. Acad. Dermatol. 55, S92–S94. doi:10.1016/j.jaad.2005.10.062

Valente, P., Axelrod, J.L., 1978. Acute leukopenia associated with silver sulfadiazine therapy. J. Trauma 18, 146–7.

Van de Voorde, K., Nijsten, T., Schelfhout, K., Moorkens, G., Lambert, J., 2005. Long-term use of silver containing nose-drops resulting in systemic argyria. Acta Clin. Belg. 60, 33–5. doi:10.1179/acb.2005.008

van den Nieuwenhuijsen, I.J., Calame, J.J., Bruynzeel, D.P., 1988. Localized argyria caused by silver earrings. Dermatologica 177, 189–91.

Viala, J., Simon, L., Le Pommelet, C., Philippon, L., Devictor, D., Huault, G., 1997. [Agranulocytosis after application of silver sulfadiazine in a 2-month old infant]. Arch. pédiatrie organe Off. la Sociéte Fr. pédiatrie 4, 1103–6.

Vlachou, E., Chipp, E., Shale, E., Wilson, Y.T., Papini, R., Moiemen, N.S., 2007. The safety of nanocrystalline silver dressings on burns: a study of systemic silver absorption. Burns 33, 979–85. doi:10.1016/j.burns.2007.07.014

Wahlberg, J.E., 1965. Percutaneous toxicity of metal compounds. A comparative investigation in guinea pigs. Arch.Environ.Health 11, 201–204.

Wan, A.T., Conyers, R.A., Coombs, C.J., Masterton, J.P., 1991. Determination of silver in blood, urine, and tissues of volunteers and burn patients. Clin. Chem. 37, 1683–7.

WHO, (WHO), W.H.O., 2008. Guidelines forDrinking-water Quality. World Health Organization (WHO), http://www.who.int/water_sanitation_health/dwq/gdwq3rev/en/.

Wilson, P., George, R., Raine, P., 1986. Topical silver sulphadiazine and profound neutropenia in a burned child. Burns. Incl. Therm. Inj. 12, 295–6.

Wollina, U., Abdel-Naser, M.B., Verma, S., 2006. Skin physiology and textiles - consideration of basic interactions. Curr. Probl. Dermatol. 33, 1–16. doi:10.1159/000093926

Yamamoto, R., Takasuga, S., Yoshida, Y., Mafune, S., Kominami, K., Sutoh, C., Kato, Y., Yamauchi, M., Ito, M., Kanamura, K., Kinoshita, M., 2012. In vitro and in vivo transdermal iontophoretic delivery of naloxone, an opioid antagonist. Int. J. Pharm. 422, 132–8. doi:10.1016/j.ijpharm.2011.10.042

Zelga, P.J., Górnicz, M.M., Głuszkiewicz, J.M., Piasecka-Zelga, J., 2016. Outcomes of acute dermal irritation and sensitisation tests on active dressings for chronic wounds: a comparative study. J. Wound Care 25, 722–729. doi:10.12968/jowc.2016.25.12.722

Zweiker, D., Horn, S., Hoell, A., Seitz, S., Walter, D., Trop, M., 2014. Semi-permanent skin staining associated with silver-coated wound dressing Acticoat. Ann. Burns Fire Disasters 27, 197–200.

Aaseth, J., Olsen, A., Halse, J., Hovig, T., 1981. Argyria—tissue deposition of silver as selenide. Scand. J. Clin. Lab. Invest. 41, 247–251. doi:10.3109/00365518109092041

Aaseth, J., Olsen, A., Halse, J., Hovig, T., 1981. Argyria-tissue deposition of silver as selenide. Scand. J. Clin. Lab. Invest. 41, 247–51. doi:10.3109/00365518109092041

Highlights

(Toxicity of silver ions, metallic silver, and silver nanoparticle materials after in vivo dermal and mucosal surface exposure: a review)

1. Silver is an ingredient in certain dermal and mucosal medical applications
2. Silver can deposit in the body as particles causing a discoloration called argyria
3. Silver is observed to have a low potential for skin irritation. Eye irritation and allergic contact dermatitis have been reported
4. Silver may cause genotoxicity, but additional data on its carcinogenic potential are required