TOXICITY SUMMARY FOR SILVER

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EXECUTIVE SUMMARY

Silver is a relatively rare metal that occurs naturally in the earth's crust and is released to the environment from various industrial sources. Human exposure to silver and silver compounds can occur orally, dermally, or by inhalation. Silver is found in most tissues, but has no known physiologic function.

In humans, accidental or intentional ingestion of large doses of silver nitrate has produced corrosive damage of the gastrointestinal tract, abdominal pain, diarrhea, vomiting, shock, convulsions, and death (U.S. EPA, 1985). Respiratory irritation was noted following acute inhalation exposure to silver or silver compounds. Silver nitrate solutions are highly irritating to the skin, mucous membranes, and eyes (Stokinger, 1981).

Ingestion, inhalation, or dermal absorption of silver may cause argyria, the most common indicator of long-term exposure to silver or silver compounds in humans. Argyria is a gray or blue-gray, permanent discoloration of the skin and mucous membranes that is not a toxic effect per se, but is considered cosmetically disfiguring. Chronic inhalation exposure of workers to silver oxide and silver nitrate dusts resulted in upper and lower respiratory irritation, deposition of granular silver-containing deposits in the eyes, impaired night vision, and abdominal pain (Rosenman et al., 1979). Mild allergic responses have been attributed to dermal contact with silver (ATSDR, 1990).

In long-term oral studies with experimental animals, silver compounds have produced slight thickening of the basement membranes of the renal glomeruli, growth depression, shortened lifespan, and granular silver-containing deposits in skin, eyes, and internal organs (Matuk et al., 1981; Olcott, 1948, 1950). Hypoactivity was seen in rats subchronically exposed to silver nitrate in drinking water (Rungby and Danscher, 1984).

A reference dose (RfD) of 0.005 mg/kg/day for subchronic and chronic exposure was calculated from a lowest-observed-adverse-effect level (LOAEL) of 0.014 mg/kg/day for argyria observed in patients receiving i.v. injections of silver arsphenamine (U.S. EPA, 1994a,b). Data are presently insufficient to derive a reference concentration (RfC) for silver (U.S. EPA, 1994a).

Data adequate for evaluating the carcinogenicity of silver to humans or animals by ingestion, inhalation, or other routes of exposure were not found. Based on U.S. EPA guidelines, silver is placed in weight-of-evidence group D, not classifiable as to human carcinogenicity (U.S. EPA, 1994a).

1. INTRODUCTION

Silver (Ag; CAS Reg. No. 7440-22-4) is a relatively rare element occurring naturally in the earth's crust as a soft, silver colored metal. It can exist in several oxidation states, with elemental silver and monovalent silver ion as the most common (ATSDR, 1990). Silver has a molecular weight of 107.868, a density of 10.5 g/cm^3 at 20°C, and a melting point of 961.93°C (Weast et al., 1988). It is insoluble in water and alkalis, but is soluble in nitric acid, hot sulfuric acid, and potassium cyanide. Some of the more common silver compounds used in industry include nitrate, chloride, bromide, acetate, oxide, sulfate, and cyanide (Stokinger, 1981).

The principal uses of silver and silver compounds are in photographic materials, electroplating, electrical conductors, dental alloys, solder and brazing alloys, paints, jewelry, coins, and mirror production. Silver is also used for cloud seeding, as an antibacterial agent, and has been used for water purification. Silver may be discharged into surface waters by various industries and accumulated in soils from the fallout emissions from coal-fired power plants. The increasing cost of the metal, however, is spurring development of recovery practices (Nordberg and Gerhardsson, 1988; U.S. EPA, 1985).

2. METABOLISM AND DISPOSITION

2.1. ABSORPTION

Studies in humans and animals indicate that silver compounds are absorbed via the oral and inhalation routes of exposure, with some absorption occurring through both intact and damaged skin (ATSDR, 1990). East et al. (1980) reported that a patient with argyria (gray or blue-gray discoloration of the skin) absorbed approximately 18% of a single dose of orally administered silver. Generalized argyria in a woman who repeatedly applied a silver nitrate solution to her gums indicates absorption across the oral mucosa (Marshall and Schneider, 1977). Absorption from the lung was documented in a case of accidental exposure to radiolabeled silver metal dust (Newton and Holmes, 1966). Following intratracheal administration to beagle dogs, the absorption of metallic silver particles appears to be extensive. Phalen and Morrow (1973) estimated that up to 90% of silver (mean aerodynamic diameter = 0.5 ：m) deposited in the lungs of dogs was absorbed into the systemic circulation 6 hours after exposure. In humans, less than 1% of topically applied silver compounds are absorbed through the skin (Snyder et al., 1975). Once deposited in the layers of the skin of humans, silver accumulates throughout the ageing process (Hostynek et al., 1993).

2.2. DISTRIBUTION

Silver has been detected in 50% of the samples of 29 human tissues, but at lower levels than other trace elements (U.S. EPA, 1985). Silver has no known physiological function in man, but its accumulation leads to argyria when the body burden is > 1 g (Stokinger, 1981). Granular deposits that contain silver have been observed in both pigmented and unpigmented skin of silver-exposed humans and animals. Once absorbed, orally-administered silver undergoes a first-pass effect through the liver, resulting in excretion into the bile, and thereby reducing the systemic distribution to tissues (ATSDR, 1990). Following ingestion of silver nitrate and silver chloride, silver was distributed widely in tissues of rats, with high concentrations seen in the tissues of the reticuloendothelial system (liver, spleen, bone marrow, lymph nodes, skin, and kidney) (Olcott, 1948). Silver was confined mainly to the liver of a worker who had accidentally inhaled radiolabeled silver metal; a biological half-life of 52 days was estimated (Newton and Holmes, 1966). Six hours after intratracheal administration of metallic silver to dogs, 96.9, 2.4, and 0.35% of the initially deposited dose was detected in the lungs, liver, and blood, respectively. The remaining silver was detected in the gall bladder and bile, intestines, and stomach. After 225 days, the distribution in tissue type was similar, with most of the silver found in the liver (Phalen and Morrow, 1976). Following intravenous injection of radioactively labeled silver nitrate, high levels of radioactivity were found in the liver and blood of rats 24 hours, and 1 and 2 weeks after treatment. The concentration of silver in the testes was about 5% of that in the liver. In the testes, deposits of silver were found in all cell types of spermatogenesis and in the lysosomes of the Sartoli cells (Ernst et al., 1991).

2.3. METABOLISM

ATSDR (1990) reports that the deposition of silver in tissues is the result of the precipitation of insoluble silver salts, such as silver chloride and silver phosphate. These insoluble silver salts are then transformed into soluble silver sulfide albuminates, to bind or to form complexes with amino or carboxyl groups in RNA, DNA, and proteins, or to be reduced by ascorbic acid or catecholamines. The skin discoloration of humans with

argyria may be caused by a photoreduction of silver chloride to metallic silver. The metallic silver is then oxidized by tissue, subsequently forming black silver sulfide.

2.4. EXCRETION

Following oral or inhalation exposure to silver compounds, humans excrete silver primarily in the feces and only very minor amounts in the urine (East et al., 1980; Newton and Holmes, 1966). In rats and mice, the cumulative recovery of silver in the feces was 98-99% on the second day after oral exposure to silver; monkeys excreted 94% (U.S. EPA, 1985). Dogs excreted approximately 90% of an inhaled dose of metallic silver particles in the feces within 30 days of exposure (Phalen and Morrow, 1973).

3. NONCARCINOGENIC HEALTH EFFECTS

3.1. ORAL EXPOSURES

3.1.1. Acute Toxicity

3.1.1.1. Human

Accidental or intentional ingestion of large doses of silver nitrate caused corrosive damage to the gastrointestinal tract, abdominal pain, diarrhea, vomiting, shock, convulsions, and death. The estimated fatal dose of silver nitrate is $ 10 g, but recoveries have been reported following ingestion of larger doses (U.S. EPA, 1985).

3.1.1.2. Animal

The acute toxicity of silver compounds appears to be high. Oral LD_{50} values for mice reported for colloidal silver and silver nitrate are 100 mg/kg and 129 mg/kg, respectively; for silver cyanide, the LD_{50} for rats is 125 mg/kg. An LD_{LO} of 2820 mg/kg for rats is reported for the relatively insoluble silver oxide (Venugopal and Luckey, 1978).

3.1.2. Subchronic Toxicity

3.1.2.1. Human

Argyria (see Section 3.1.3.1.) has been observed in individuals that have ingested both metallic silver and silver compounds in small doses over periods of months to years (ATSDR, 1990). Blumberg and Carey (1934) reported argyria in an emaciated female adult who had ingested an estimated total dose 6.4 g silver nitrate over a 1-year period. Symptoms of argyria appeared in one individual after the first 6 months of exposure to unknown quantities of silver acetate (East et al., 1980).

3.1.2.2. Animal

One study indicated that female mice exposed to silver nitrate in drinking water for 4 months were less active than controls. The mice also had granular silver-containing deposits in some areas of the central nervous system, with highest concentrations in areas involved in motor control (Rungby and Danscher, 1984).

3.1.3. Chronic Toxicity

3.1.3.1. Human

Argyria, a characteristic and irreversible gray or blue-gray discoloration of the skin and mucous membranes, has been observed in individuals that have ingested both metallic silver and silver compounds in small doses over periods of months or years. Argyria, both generalized or localized, has resulted from such uses as antismoking lozenges containing silver acetate, breath mints coated with silver, silver nitrate solutions for the treatment of gum disease, and silver nitrate capsules for relief of gastrointestinal discomfort (ATSDR, 1990; Stokinger, 1981). Argyria is most noticeable in areas of skin exposed to light (ATSDR, 1990) and blond individuals are considered more susceptible to argyria than others (Nordberg and Gerhardsson, 1988). The pigmentation is not a toxic effect per se, but can be considered a cosmetic disfigurement in some cases. Silver-containing granules, particularly concentrated in basement membranes and elastic fibers surrounding sweat glands, have been observed during histopathologic examination of the skin of these individuals (ATSDR, 1990). When argyria is localized in the eyes, the conjunctiva is most frequently affected, with silver deposition on the elastic fibers (Stokinger, 1981). The estimated total dose required to induce argyria by ingestion is in the range of 1-30 g for soluble silver salts (Nordberg and Gerhardsson, 1988).

3.1.3.2. Animal

Exposure of rats to 222 mg silver/kg/day in drinking water for 37 weeks resulted in growth depression and shortened lifespan. Also observed were granular silver deposits in the eyes (Matuk et al., 1981).

Olcott (1948, 1950) reported enlargement of the left ventricle of the heart in rats receiving drinking water containing 635-660 mg silver/day as either silver nitrate or silver chloride for life. Histologic examination showed slight thickening of the basement membranes of kidney glomeruli in the absence of severe renal lesions. Deposition of silver granules was observed in the skin, eyes, and several internal organs.

3.1.4. Developmental and Reproductive Toxicity

3.1.4.1. Human

Information on the developmental and reproductive toxicity in humans following inhalation exposure to silver was not available.

3.1.4.2. Animal

There was no decrease of fertility in male rats exposed for life to drinking water containing 635-660 mg silver/day as either silver nitrate or silver chloride (Olcott, 1948).

3.1.5. Reference Dose

3.1.5.1. Subchronic

ORAL RfD: 0.005 mg/kg/day (U.S. EPA, 1994b)
UNCERTAINTY FACTOR: 3
LOAEL: 0.014 mg/kg/day

COMMENT: The chronic RfD was adopted as the subchronic RfD.

3.1.5.2. Chronic

ORAL RfD: 0.005 mg/kg/day (U.S.EPA, 1994a,b)
UNCERTAINTY FACTOR: 3
LOAEL: 0.014 mg/kg/day

CONFIDENCE:
Study: Medium
Data Base: Low
RfD: Low

VERIFICATION DATE: 7/18/91

PRINCIPAL STUDY: Gaul and Straud, 1935

COMMENTS: The LOAEL is based on argyria observed in humans administered i.v. injections of silver arsphenamine over a 2- to 9-year period. The total i.v. dose of 1 g (as silver) was converted to a total oral dose of 25 g (i.v. dose divided by 0.04, the assumed oral retention factor) and dividing by 70 kg (adult body weight) and 25,500 days. The uncertainty factor is applied to protect sensitive human subpopulations.

3.2. INHALATION EXPOSURES

3.2.1. Acute Toxicity

3.2.1.1. Human

Acute irritation of the respiratory tract can occur from inhalation of silver nitrate dust, but generally only at concentrations that produce argyria (Stokinger, 1981). One case report described severe respiratory effects in a worker who had become ill 14 hours after working with molten silver ingots (Forycki et al., 1983).

3.2.1.2. Animal

Acute inhalation (2-8 hours) of an aerosol containing colloidal silver caused ultrastructural damage and disruption of cells of the tracheal epithelium of rabbits (ATSDR, 1990).

3.2.2. Subchronic Toxicity

Because the available human inhalation studies do not permit a clear distinction between subchronic and chronic effects, the data are presented only in Section 3.2.3.1., Chronic Toxicity.

3.2.2.2. Animal

Information on the subchronic inhalation toxicity of silver in animals was not available.

3.2.3. Chronic Toxicity

3.2.3.1. Human

Generalized argyria has been reported in workers associated with manufacturing and packaging of silver nitrate and in workers engaged in mining, smelting, polishing, and hammering of silver (U.S. EPA, 1985). Argyria may be localized in the respiratory tract, with isolated areas of pigmentation occurring at the tracheobronchial junction and around the orifices of the smaller bronchi in more severe cases (Stokinger, 1981). The estimated total dose required to induce argyria by inhalation is in the range of 1-8 g for soluble silver salts (Nordberg and Gerhardsson, 1988).

Rosenman et al. (1979) reported that 25/30 workers exposed to silver nitrate and silver oxide dusts for < 1 to > 10 years experienced respiratory irritation (sneezing, stuffiness, and running nose or sore throat) at some time during their employment. Cough, wheezing, chest tightness, and abdominal pain were reported in 20/30 workers. The abdominal pain was significantly correlated with blood silver levels. Granular silver-containing deposits, observed in the conjunctiva and cornea of the eyes of 20/30 workers, correlated with the duration of employment. Decreased night vision was recorded in some workers. The exposure levels (8-hour time-weighted average), determined 4 months prior to the study, ranged from 0.039 to 0.378 mg silver/m^3.

Decreased night vision was also reported in a group of workers manufacturing metal silver powder (Rosenman et al., 1987). Also seen was increased excretion of the kidney enzyme N-acetyl-ß-D-glucosaminidase and decreased creatinine clearance, suggestive of impaired kidney function. However, the workers were also exposed to cadmium, a known nephrotoxic compound.

In a study with silver reclamation workers exposed to silver and insoluble silver compounds, conjunctival and corneal argyria was seen in 21% and 25% of the workers, respectively (Pifer et al., 1989). Many of the workers exhibited internal nasal-septal pigmentation. There were no significant differences in the levels of several liver enzymes between exposed individuals and those with no history of silver exposure.

3.2.3.2. Animal

Information on the chronic inhalation toxicity of silver in animals was not available.

3.2.4. Developmental and Reproductive Toxicity

Information on the developmental and reproductive toxicity in humans or animals following inhalation to silver was not available.

3.2.5. Reference Concentration

Data were insufficient to derive a reference concentration (RfC) for silver.

3.3. OTHER ROUTES OF EXPOSURE

3.3.1. Acute Toxicity

3.3.1.1. Human

Metallic silver is not considered highly allergenic, but isolated cases of immediate or delayed contact dermatitis have been reported (Hostynek et al., 1993). Silver nitrate solutions are highly irritating to the skin, mucous membranes, and eyes. Ocular damage has been reported from application of solutions containing > 2% silver nitrate. Corneal opacification may be so severe as to cause blindness. Application of silver nitrate to the gingiva may result in necrotizing, ulcerative gingivitis (Stokinger, 1981).

3.3.1.2. Animals

Early studies reported effects on the nervous system, including weakness, rigidity of legs, loss of voluntary movement, and respiratory paralysis following intravenous administration of high doses of silver compounds to rats, dogs, and guinea pigs (U.S. EPA, 1985). Intravenous administration of 25.2 mg/kg silver nitrate, 420 mg/kg colloidal silver, or 11.6 mg/kg silver proteinate resulted in the death of rats within 24-48 hours (Dequidt et al., 1974).

3.3.2. Subchronic Toxicity

3.3.2.1. Human

Intravenous administration of an estimated total dose of 4-20 g silver arsphemamine over a 2- to 9.75-year period caused argyria in humans. Argyria developed after a total dose of 4-8 g in some patients, while in others argyria did not develop until after a total dose of 10-20 g (Gaul and Straud, 1935).

3.3.2.2. Animal

Guinea pigs ceased to gain weight when a 0.239 molar solution of silver nitrate was applied to 3.1 cm^2 of skin for 8 weeks (Wahlberg, 1965).

3.3.3. Chronic Toxicity

3.3.3.1. Human

Case histories indicate that dermal exposure to silver or silver compounds for extended periods can lead to generalized skin discoloration similar to that seen after oral exposure. Also reported were mild allergic responses attributed to dermal contact with silver or silver compounds. Sensitization has resulted from contact with powdered silver cyanide, radiographic processing solutions containing silver compounds, and to silver in dental amalgam (ATSDR, 1990).

3.3.4. Developmental and Reproductive Toxicity

3.3.4.1. Human

Information on the developmental and reproductive toxicity in humans by other routes of exposure to silver was not available.

3.3.4.2. Animal

A single subcutaneous injection of 0.04 millimole/kg silver nitrate caused temporary histopathological damage to testicular tissue of male rats (Hoey, 1966).

3.4. TARGET ORGANS/CRITICAL EFFECTS
3.4.1. Oral Exposures
3.4.1.1. Primary Target Organs

Skin and mucous membranes: Argyria, both general and localized, is the most common effect of chronic exposure to silver and silver compounds in humans. Granular silver-containing deposits are seen in animals.

3.4.1.2. Other Target Organs

1. Heart: Chronic exposure of rats caused enlargement of the left ventricle of the heart.

2. Kidneys: Chronic exposure of rats caused a slight thickening of the basement membranes of the renal glomeruli.

3. Central nervous system: Hypoactivity was observed in rats subchronically exposed to silver.

3.4.2. Inhalation Exposures

3.4.2.1. Primary Target Organs

1. Skin and mucous membranes: Argyria, both general and localized, is the most common effect of chronic inhalation exposure to silver in humans.

2. Respiratory tract: Occupational exposure to silver has caused upper and lower respiratory tract irritation.

3.4.2.2. Other Target Organs

1. Eyes: Impairment of night vision was reported in some workers chronically exposed to silver.
2. Kidneys: An occupational study suggests impairment of kidney function as evidenced by increased excretion of a kidney enzyme indicative of cellular damage and by decreased creatinine clearance.

3. Gastrointestinal tract: Abdominal pain was one of the symptoms recorded in workers exposed to silver.

4. CARCINOGENICITY
4.1. ORAL EXPOSURES

Information on the oral carcinogenicity of silver in humans or animals was not available.

4.2. INHALATION EXPOSURES

Information on the carcinogenicity of inhaled silver in humans or animals was not available.

4.3. OTHER ROUTES OF EXPOSURE
4.3.2. Human
4.3.1. Animal

Subcutaneous embedding of silver foil induced a 32% incidence of local fibrosarcomas in rats, with a latency period of 275 days (Oppenheimer et al., 1956). Silver apparently produced fibrosarcomas earlier and more frequently than several other metal foils. Schmähl and Steinhoff (1960) reported that colloidal silver injected subcutaneously into rats resulted in tumors in 8/26 rats that survived longer than 14 months. In six of the eight rats, the tumors were at the injection site. However, use of the subcutaneous route of exposure is questionable, because almost any implanted solid may induce a fibrosarcoma at the site (Furst, 1981). In another study, no tumors were found at the injection site of rats intramuscularly injected with silver (Furst and Schlauder, 1977).

4.4. EPA WEIGHT-OF-EVIDENCE

Classification D -- Not classifiable as to human carcinogenicity (U.S. EPA, 1994a)
Basis -- In animals, local sarcomas have been induced after implantation of foils and discs of silver. However, the interpretation of these findings has been questioned due to the phenomenon of solid-state carcinogenesis in which even insoluble solids such as plastics have been shown to result in local fibrosarcomas (U.S. EPA, 1994a).

4.5. CARCINOGENICITY SLOPE FACTORS

None were calculated.

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