
A Review of Toxicity and Epidemiological Data for Silver in Animals and Humans

Daland R. Juberg
Eastman Kodak Company
Rochester, New York, USA

While regulatory efforts to control the release and transport of silver in the environment are initially aimed at protection of aquatic life and ecosystem health, such efforts are also intended for the protection of human health. Therefore, it is important to consider available mammalian toxicity and human epidemiology data for silver when assessing and prioritizing potential hazards to public health. This abstract will review (1) toxicity data for silver in animals, focusing primarily on oral studies using soluble forms of silver, (2) epidemiological studies involving occupational exposures to silver, and (3) the derivation of the U.S. Environmental Protection Agency's (EPA) Secondary Maximum Contaminant Level (SMCL) for silver in drinking water.

Acute oral LD₅₀ studies using silver nitrate, silver oxide, silver fluoride, and silver chloride in various animal species have reported LD₅₀ values in dose ranges that are considered indicative of slight to moderate toxicity. In subchronic drinking water studies with animals given soluble forms of silver (primarily silver nitrate), effects reported following exposure to 0.015 to 0.02% silver included deposition of silver grains in the conjunctiva (rat) and kidneys (rat), and hypoactivity (mice). It should be noted that these effects have not been consistently reported or observed in other animal studies. Additionally, the lowest observed effect level tested in animals (0.015%) from these studies is 1500 times greater than the current SMCL for silver in drinking water. Although silver deposits in various organs in animals, it is not associated with target organ toxicity.

In humans, acute occupational exposure to silver nitrate has been associated with skin, eye, and respiratory irritation, most notably at high airborne concentrations. Chronic silver exposure in humans has not been associated with target organ toxicity and no

significant hematological or hepatic effects have been reported in two occupational studies involving exposure to both soluble and insoluble silver. Epidemiological studies typically evaluate chronic exposures and are useful and considered more relevant than animal data when evaluating potential health effects in humans. For silver, there are several adequate epidemiology studies. The available studies have involved exposure to numerous silver species (silver nitrate, silver oxide, metallic silver, insoluble silver halides) at estimated air concentrations ranging from 0.001 to 0.378 mg/m³ as 8-hr time weighted averages. Duration of exposure in terms of years of employment ranged from 5 to 20 years. Our experience involving silver reclamation employees has shown increased levels of silver in blood, feces, and hair with no evidence of adverse health effects. In addition, respiratory function and clinical chemistry (hematology indices, hepatic enzyme levels) analyses were not different from referent groups. The principal effect observed in our study and in other epidemiological investigations is argyria, a condition characterized by bluish-gray pigmentation of the skin, mucous membranes, and eyes (primarily conjunctiva).

Argyria results from tissue deposition of a silver-protein complex or its metabolized product (silver sulfide or silver selenide) following long-term exposure (absorbed amounts in excess of 1 g) to silver or silver-containing compounds. Argyrosis is a term that refers to ocular silver deposition while argyria describes the systemic distribution of silver that manifests itself as pigmentation of those sites most exposed to sunlight. Argyria occurs most commonly following airborne exposure in occupational settings; the only cases of argyria resulting from ingestion of silver-containing compounds occurred in individuals, usually with compromised health status, taking oral medications containing high concentrations of silver. Argyria or argyrosis have not been reported as a result of exposure to silver in the environment. Most importantly, argyria and argyrosis have not been associated with adverse health effects or compromised health status and are considered cosmetic effects by the EPA.

Silver is not extensively metabolized in mammalian species and this may contribute to its low degree of toxicity in animals and humans. Silver is associated with low absorption (less than 10% of administered or ingested dose in animals) although the presence and extent of silver-binding proteins and the solubility of the particular silver species are important modifiers of absorption. Once absorbed, silver passes through the liver and spleen and if not eliminated, is then systemically distributed. Elimination of silver from the body is primarily (> 90%) through fecal excretion with urinary excretion only a minor

factor in clearance of silver from the body. The half-life of silver in the lungs and liver is approximately 1 day and 50 days, respectively.

In 1991, EPA deleted the Primary Drinking Water Standard of 50 $\mu\text{g/L}$ silver and replaced it with a SMCL of 100 $\mu\text{g/L}$ based on the endpoint of argyria. The derivation of this number included the following assumptions: (a) the development of argyria in the most sensitive individual could occur following absorption of 1 g of silver (based on clinical case reports); (b) the oral absorption rate is 4%; (c) the exposure period is 70 years; and (d) the body weight is 70 kg. In addition, it is assumed that 100% of a person's silver intake is from drinking water and that the average person ingests 2 L of water per day. A cosmetic reference dose (safe exposure level) is generated, which includes a safety factor of 3. Finally, an adjustment (subtraction from that amount permitted in drinking water) is included for the presence, and assumed ingestion, of silver in food. In addition to EPA, both the American Conference of Governmental Industrial Hygienists and the Occupational Safety and Health Administration have established permissible air exposure limits for silver based on the development of argyria as the endpoint of concern.

In summary, although some species of silver are irritating, e.g., silver nitrate, the only significant effect from exposure to silver is argyria, a cosmetic effect, which does not impair the functioning of the body. A number of occupational studies of employees exposed to silver have clearly indicated that this cosmetic effect is limited to the skin and mucous membranes without evidence of health impairment. Our recent epidemiology study in silver reclamation employees confirmed these findings. Regulatory and standard setting organizations have used argyria as the endpoint for establishing acceptable exposure levels for both occupationally exposed employees and the general public.

Questions & Answers: A Review of Toxicity and Epidemiological Data for Silver in Animals and Humans

- Q. ERIC CRECELIUS (Battelle): Do you have any speculation on why silver seems to be that way?
- A. I guess the answer to that question is, I've thought about it. Certainly the insoluble nature of many silver compounds, combined with the fact that it does not seem to target a particular organ, may be keys to its lack of human toxicity. It's certain that some of the other metals do target specific organs, such as lead — it's a soft tissue toxicant, a liver toxicant. Cadmium is a known kidney toxicant and tends to bind there and exert effects, although a lot of it may still be insoluble. With silver, we're not adsorbing enough and it just doesn't exert clear toxicity.
- Q. CHRIS WOOD (McMaster Univ.): Is there any information of exactly how it's carried? You just said it is not excreted at all in the urine, so does that mean it is bound to proteins, or is it in cells? What form is it in the blood in occupationally exposed people?
- A. That's a good question, Chris. I don't know the answer to that. It is carried by proteins, so it must be in cytoplasm. As to the form, I don't know. That's clearly an important system to look at and why some of those occupational studies have focused in on that and say it's a site of potential toxicity. Again, only solubilized silver can enter the bloodstream.
- Q. JIM KRAMER (McMaster Univ.): Maybe you said that and I missed it. In going through the logic of studying the drinking water, food, and so on, is that the logic that assumes all the silver — or is that the total silver level or any silver in particles, wherever it is — will be reactive?
- A. You mean, is this all of the silver a person will be exposed to?
- Q. Yes. In going through the calculation you showed us, that assumes all of the silver will be effective?
- A. Certainly, right.