Silver; CASRN 7440-22-4

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Silver

File First On-Line 01/31/1987

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<th>Last Revised</th>
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<td>12/01/1991</td>
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I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Silver
CASRN — 7440-22-4
Last Revised — 12/01/1991

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of
information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

**I.A.1. Oral RfD Summary**

<table>
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<tr>
<th>Critical Effect</th>
<th>Experimental Doses*</th>
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<th>MF</th>
<th>RfD</th>
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<td>Argyria</td>
<td>NOEL: None</td>
<td>3</td>
<td>1</td>
<td>5E-3 mg/kg/day</td>
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<tr>
<td>2- to 9-Year Human i.v. Study</td>
<td>LOAEL: 1 g (total dose); converted to an oral dose of 0.014 mg/kg/day</td>
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*Conversion Factors: Based on conversion from the total i.v. dose to a total oral dose of 25 g (i.v. dose of 1 g divided by 0.04, assumed oral retention factor; see Furchner et al., 1968 in Additional Comments section) and dividing by 70 kg (adult body weight) and 25,500 days (a lifetime, or 70 years).

**I.A.2. Principal and Supporting Studies (Oral RfD)**


The critical effect in humans ingesting silver is argyria, a medically benign but permanent bluish-gray discoloration of the skin. Argyria results from the deposition of silver in the dermis and also from silver-induced production of melanin. Although silver has been shown to be uniformly deposited in exposed and unexposed areas, the increased pigmentation becomes more pronounced in areas exposed to sunlight due to photoactivated reduction of the metal. Although the deposition of silver is permanent, it is not associated with any adverse health effects. No pathologic changes or inflammatory reactions have been shown to result from silver deposition. Silver compounds have been employed for medical uses for centuries. In the nineteenth and early twentieth centuries, silver arsphenamine was used in the treatment of syphilis; more recently it has been used as an astringent in topical preparations. While argyria occurred more commonly before the development of antibiotics, it is now a rare occurrence. Greene and Su (1987) have published a review of argyria.
Gaul and Staud (1935) reported 70 cases of generalized argyria following organic and colloidal silver medication, including 13 cases of generalized argyria following intravenous silver arsphenamine injection therapy and a biospectrometric analysis of 10 cases of generalized argyria classified according to the quantity of silver present. In the i.v. study, data were presented for 10 males (23-64 years old) and for two females (23 and 49 years old) who were administered 31-100 i.v. injections of silver arsphenamine (total dose was 4-20 g) over a 2- to 9.75-year period. Argyria developed after a total dose of 4, 7 or 8 g in some patients, while in others, argyria did not develop until after a total dose of 10, 15 or 20 g. In the biospectrometric analysis of skin biopsies from 10 cases of generalized argyria, the authors confirmed that the degree of the discoloration is directly dependent on the amount of silver present. The authors concluded that argyria may become clinically apparent after a total accumulated i.v. dose of approximately 8 g of silver arsphenamine. The book entitled "Argyria. The Pharmacology of Silver" reached the same conclusion, that a total accumulative i.v. dose of 8 gm silver arsphenamine is the limit beyond which argyria may develop (Hill and Pillsbury, 1939). However, since body accumulates silver throughout life, it is theoretically possible for amounts less than this (for example, 4 g silver arsphenamine) to result in argyria. Therefore, based on cases presented in this study, the lowest i.v. dose resulting in argyria in one patient, 1 g metallic silver (4 g silver arsphenamine x 0.23, the fraction of silver in silver arsphenamine) is considered to be a minimal effect level for this study.

Blumberg and Carey (1934) reported argyria in an emaciated chronically ill (more than 15 years) 33-year-old female (32.7 kg) who had ingested capsules containing silver nitrate over a period of 1 year. The patient reported ingesting 16 mg silver nitrate three times a day (about 30 mg silver/day) for alternate periods of 2 weeks. Spectrographic analysis of blood samples revealed a blood silver level of 0.5 mg/L 1 week after ingestion of silver nitrate capsules ceased, and there was only a small decrease in this level after 3 months. The authors noted that this marked argyremia was striking because even in cases of documented argyria, blood silver levels are not generally elevated to this extent. Normal levels for argyremic patients were reported to range from not detected to 0.005 mg Ag/l blood. Heavy traces of silver in the skin, moderate amounts in the urine and feces, and trace amounts in the saliva were reported in samples tested 3 months after ingestion of the capsules stopped; however, despite the marked argyremia and detection of silver in the skin, the argyria at 3 months was quite mild. No obvious dark pigmentation was seen other than gingival lines which are considered to be characteristic of the first signs of argyria. The authors suggested that this may have been because the woman was not exposed to strong light during the period of silver treatment. This study is not suitable to serve as the basis for a quantitative risk assessment for silver because it is a clinical report on only one patient of compromised health. Furthermore, the actual amount of silver ingested is based on the patient's recollection and cannot be accurately determined.
In a case reported by East et al. (1980), argyria was diagnosed in a 47-year-old woman (58.6 kg) who had taken excessively large oral doses of anti-smoking lozenges containing silver acetate over a period of 2.5 years. No information was provided as to the actual amount of silver ingested. Symptoms of argyria appeared after the first 6 months of exposure. Based on whole body neutron activation analysis, the total body burden of silver in this female was estimated to be 6.4 (plus or minus 2) g. Both the total body burden and concentration of silver in the skin were estimated to be 8000 times higher than normal. In a separate 30-week experiment, the same subject retained 18% of a single dose of orally-administered silver, a retention level much higher than that reported by other investigators. East et al. (1980) cited other studies on this particular anti-smoking formulation (on the market since 1973) which demonstrated that "within the limits of experimental error, no silver is retained after oral administration." However, this may not hold true for excessive intakes like that ingested by this individual. As with the study by Blumberg and Carey (1934), this study is not suitable to serve as the basis for a quantitative risk assessment. It is a clinical report on only one patient and the actual amount of silver ingested can only be estimated.

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF — An uncertainty factor of 3 is applied to account for minimal effects in a subpopulation which has exhibited an increased propensity for the development of argyria. The critical effect observed is a cosmetic effect, with no associated adverse health effects. Also, the critical study reports on only 1 individual who developed argyria following an i.v. dose of 1 g silver (4 g silver arsphenamine). Other individuals did not respond until levels five times higher were administered. No uncertainty factor for less than chronic to chronic duration is needed because the dose has been apportioned over a lifetime of 70 years.

MF — None

I.A.4. Additional Studies/Comments (Oral RfD)

In the study by East et al. (1980) (see section 1.A.2.), one human was found to retain 18% of a single oral dose. However, the authors acknowledge that this high level of retention is not consistent with data published in other laboratories. For ethical reasons, the experiment could not be repeated to determine the validity of the results.

Humans are exposed to small amounts of silver from dietary sources. The oral intake of silver from a typical diet has been estimated to range from 27-88 ug/day (Hamilton and Minski, 1972/1973; Kehoe et al., 1940). Tipton et al. (1966) estimated a lesser intake of 10-20 ug/day in two subjects during a 30-day observation period. Over a lifetime, a small but measurable amount of silver is accumulated by individuals having no excessive exposure. Gaul and Staud
(1935) estimated that a person aged 50 years would have an average retention of 0.23-0.48 g silver (equivalent to 1-2 g silver arsphenamine). Petering et al. (1991) estimated a much lower body burden of 9 mg over a 50-year period based on estimated intake, absorption, and excretion values; however, it is not clear how the final estimate was calculated. Furchner et al. (1968) studied the absorption and retention of ingested silver (as silver nitrate, amount not specified) in mice, rats, monkeys and dogs. In all four species, very little silver was absorbed from the GI tract. Cumulative excretion ranged from 90 to 99% on the second day after ingestion, with <1% of the dose being retained in <1 week in monkeys, rats and mice. Dogs had a slightly greater retention. The authors used the data from the dog to estimate how much silver ingested by a 70 kg human would be retained. An "equilibrium factor" of 4.4% was determined by integrating from zero to infinity a retention equation which assumes a triphasic elimination pattern for silver with the initial elimination of 90% coming from the dog data. The first elimination half-time of 0.5 days was used "arbitrarily"; subsequent half-times of 3.5 days and 41 days were taken from a metabolic study by Polachek et al. (1960). Furchner et al. (1968) considered their calculated equilibrium factor of 4.4% to be a conservative estimate for the amount of silver which would be retained by a 70 kg human. This figure was rounded to 4% and was used in the dose conversion (i.v. dose converted to oral intake) for the calculation of the RfD.

In addition to silver arsphenamine, any silver compound (silver nitrate, silver acetate, argyrol, Neosilvol and Collargol, etc.), at high dose, can cause argyria. Another important factor predisposing to the development of argyria is the exposure of the skin to light.

Argyria, the critical effect upon which the RfD for silver is based, occurs at levels of exposure much lower than those levels associated with other effects of silver. Argyrosis, resulting from the deposition of silver in the eye, has also been documented, but generally involves the use of eye drops or make-up containing silver (Greene and Su, 1987). Silver has been found to be deposited in the cornea and the anterior capsule of the lens. The same deposition pattern was seen in the eyes of male Wistar rats following administration of a 0.66% silver nitrate solution to the eyes for 45 days (Rungby, 1986). No toxicological effects were reported.

Toxic effects of silver have been reported primarily for the cardiovascular and hepatic systems. Olcott (1950) administered 0.1% silver nitrate in drinking water to rats for 218 days. This exposure (about 89 mg/kg/day) resulted in a statistically significant increase in the incidence of ventricular hypertrophy. Upon autopsy, advanced pigmentation was observed in body organs, but the ventricular hypertrophy was not attributed to silver deposition.

Hepatic necrosis and ultrastructural changes of the liver have been induced by silver administration to vitamin E and/or selenium deficient rats (Wagner et al., 1975; Diplock et al., 1967; Bunyan et al., 1968). Investigators have hypothesized that this toxicity is related to a silver-induced selenium deficiency that inhibits the synthesis of the seleno-enzyme glutathione.

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Integrated Risk Information System (IRIS)  
Chemical Assessment Summary  
U.S. Environmental Protection Agency  
National Center for Environmental Assessment
peroxidase. In animals supplemented with selenium and/or vitamin E, exposures of silver as high as 140 mg/kg/day (100 mg Ag/L drinking water) were well-tolerated (Bunyan et al., 1968).

I.A.5. Confidence in the Oral RfD

Study — Medium
Database — Low
RfD — Low

The critical human study rates a medium confidence. It is an old study (1935) which offers fairly specific information regarding the total dose of silver injected over a stated period of time. One shortcoming of the study is that only patients developing argyria are described; no information is presented on patients who received multiple injections of silver arsphenamine without developing argyria. Therefore, it is difficult to establish a NOAEL. Also, the individuals in the study were being treated for syphilis and may have been of compromised health.

Confidence in the database is considered to be low because the studies used to support the RfD were not controlled studies. For clinical case studies of argyria (such as Blumberg and Carey, 1934; East et al., 1980), it is especially difficult to determine the amount of silver that was ingested.

Confidence in the RfD can be considered low-to-medium because, while the critical effect has been demonstrated in humans following oral administration of silver, the quantitative risk estimate is based on a study utilizing intravenous administration and thus necessitates a dose conversion with inherent uncertainties.

I.A.6. EPA Documentation and Review of the Oral RfD

Source Document — This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation — None


Verification Date — 07/18/1991

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for silver conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new
studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Silver
CASRN — 7440-22-4

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Silver
CASRN — 7440-22-4
Last Revised — 06/01/1989

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.
II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Classification — D; not classified as to human carcinogenicity

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 plastic have been shown to result in local fibrosarcomas.

II.A.2. Human Carcinogenicity Data

No evidence of cancer in humans has been reported despite frequent therapeutic use of the compound over the years.

II.A.3. Animal Carcinogenicity Data

Inadequate. Local sarcomas have been induced after subcutaneous (s.c.) implantation of foils and discs of silver and other noble metals. Furst (1979, 1981), however, cited studies showing that even insoluble solids such as smooth ivory and plastic result in local fibrosarcomas and that tin when crumbled will not. He concluded that i.p. and s.c. implants are invalid as indicators of carcinogenicity because a phenomenon called solid-state carcinogenesis may complicate the interpretation of the cause of these tumors. It is difficult to interpret these implantation site tumors in laboratory animals in terms of exposure to humans via ingestion. Within these constraints there are two studies given below in which silver per se appeared to induce no carcinogenic response.

Schmahl and Steinhoff (1960) reported, in a study of silver and of gold, that colloidal silver injected both i.v. and s.c. into rats resulted in tumors in 8 of 26 rats which survived longer than 14 months. In 6 of the 8, the tumor was at the site of the s.c. injection. In about 700 untreated rats the rate of spontaneous tumor formation of any site was 1 to 3%. No vehicle control was reported.

Furst and Schlauder (1977) evaluated silver and gold for carcinogenicity in a study designed to avoid solid-state carcinogenesis. Metal powder was suspended in trioctanoin and injected monthly, i.m., into 50 male and female Fischer 344 rats per group. The dose was 5 mg each for 5 treatments and 10 mg each for 5 more treatments for a total dose of 75 mg silver. The treatment regimen included a vehicle control (a reportedly inert material), and cadmium as a positive control. Injection site sarcomas were found only in vehicle control (1/50), gold (1/50) and
cadmium (30/50); no tumors (0/50) appeared at the site of injection in the silver-treated animals. A complete necropsy was performed on all animals. The authors mentioned the existence of spontaneous tumors in Fischer 344 rats, but reported only injection site tumors. They concluded that finely divided silver powder injected i.m. does not induce cancer.

II.A.4. Supporting Data for Carcinogenicity

Further support for the lack of silver's ability to induce or promote cancer stems from the finding that, despite long standing and frequent therapeutic usage in humans, there are no reports of cancer associated with silver. In a recent Proceedings of a Workshop/Conference on the Role of Metals in Carcinogenesis (1981) containing 24 articles on animal bioassays, epidemiology, biochemistry, mutagenicity, and enhancement and inhibition of carcinogenesis, silver was not included as a metal of carcinogenic concern.

No evidence of the mutagenicity of silver was shown in two available studies. Demerec et al. (1951) studied silver nitrate for the possible induction of back-mutations from streptomycin dependence to nondependence in Eschericha coli. Silver nitrate was considered nonmutagenic in this assay. Nishioka (1975) screened silver chloride with other chemicals for mutagenic effects using a method called the rec-assay. Silver chloride was considered nonmutagenic in this assay.

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

Not available.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

Not available.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation


The 1988 Drinking Water Criteria Document for Silver has received Agency Review.
II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Work Group Review — 09/22/1988

Verification Date — 09/22/1988

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for silver conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

III. [reserved]

IV. [reserved]

V. [reserved]

VI. Bibliography

Substance Name — Silver
CASRN — 7440-22-4

VI.A. Oral RfD References


VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References


VII. Revision History

Substance Name — Silver
CASRN — 7440-22-4

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VIII. Synonyms

Substance Name — Silver
CASRN — 7440-22-4
Last Revised — 06/01/1989

- 7440-22-4
- ARGENTUM CREDE
- COLLARGOL
- Silver