SILVER 100™ SAFETY REPORT

Invision International, Inc.
January 9, 1999
by
Jay Newman and Robert Tuck

Purpose: This report was prepared by Invision International to demonstrate the safety of its Silver 100™ Ionic Silver Complex by citing current U.S. government regulations and reports.

Sources: The information relied upon in this report is obtained from the following sources:

DWRHA	Drinking Water Regulations and Health Advisories, Office of Water, U.S. EPA
HADWC	Health Advisories for Drinking Water Contamination, U.S. EPA
ATSDR	Toxicological Profile for Silver, Agency for Toxic Substances and Disease Registry, Public Health Service, U.S. Department of Health & Human Services
EPA IRIS	Integrated Risk Information System, U.S. EPA

DWRHA – This is the law in the U.S. as of the date hereof with respect to safe levels of silver, both in terms of total overall intake and in terms of safe concentrations for drinking water. It was issued October 1996. Although the guidelines call for an update of this document every six months, no update has occurred in the past two years, consistent with the conclusions that silver is quite safe at given levels.

HADWC – This is a book covering the safety of drinking water. The document to which we make reference is actually the original material that one of the co-authors of the book, Dr. Julie Du, who is apparently EPA's top expert on silver, provided to the publishers as her expert contribution for the section on silver. We spoke at length with Dr. Du and went over all the math with her. Her report is dated April 1992. The book was published in 1993.

ATSDR – This is a 145-page book on the safety of silver, published in December 1990.

EPA IRIS – This is a non-regulatory summary from EPA on the safety of silver, dated March 1, 1997.

Exhibits: Included herewith are copies of selected pages from the documents described above. The extensive handwritten notes on those copies are mostly by Robert Tuck, Invision International's head scientist, who conducted most of the research for this report, and some are by Jay Newman, president of Invision International.

Page Numbering: The copies of documents in the Exhibits section contain original page numbers where they existed, as well as the page number appropriate to the sequential order of those pages herein. In order to facilitate clarity, page numbers that apply to the sequence of pages as they appear in this Report are enclosed in brackets ("[#]"without the quotes). All references herein to page numbers in the Exhibits specify the original document and page number proper to that document, and then the page number proper to the sequence of pages in this Report, which follows in brackets.

SUMMARY

Due to the obvious lack of toxicity and overall harmlessness of silver, in 1991 EPA not only doubled the recommended limit for silver in drinking water but also discarded the previous "enforceable regulation" and made the new recommended limit an "unenforceable guideline." See HADWC, page 15, paragraph V (page [14] hereof).

There are officially no health concerns regarding silver intake, except, of course, at such severe extremes where even the most "harmless" of substances can become dangerous. The limits targeted for lifelong silver intake pertain to a harmless but nonetheless undesirable cosmetic effect called "argyria" which entails a permanent gray discoloration of the skin. Those limits are far below the levels that would be required to pose any other type of health concerns. See EPA IRIS, page 5 (page [21] hereof).

The most sensitive individual can be considered to be free from risk of developing early stages of argyria if the total quantity of silver taken orally over their lifetime does not exceed 25 grams (assuming, of course, there is not a substantial amount of silver exposure through other means). See HADWC, page 14, paragraph E (page [13] hereof). Safety levels are more precisely ascertained in terms of body weight.

Assuming even the highest levels of normal silver intake from diet and drinking water, an individual taking the maximum recommended daily amount of Silver 100™ Ionic Silver Complex every day for seventy years would have ingested far less total silver during their lifetime than it would take for anyone to be at risk of developing even the earliest stages of argyria. (See Calculations, below, and all Exhibits.)

Note: There is, of course, no possibility of accommodating cases in which individuals are exposed to excessively high amounts of silver, such as through injection or industrial exposure to silver.

Comments

DWRHA contains two key figures: Reference Dose (RfD), which is the recommended daily limit, on page 9 (page [9] hereof), and Secondary Maximum Contaminant Level (SMCL), which is under Drinking Water Standards and Health Advisory on page 10 (page [10] hereof).

We consider the RfD (see Calculations, page [3] hereof, and see also page [7] hereof) crucial and of primary significance in understanding the government guidelines regarding silver limitations in the diet, recognizing that it deliberately addresses only the cosmetic effect, argyria.

We further consider the SMCL to be of pivotal importance in that it represents the closest thing to current legal limits on allowable silver levels in our drinking water, and the most pronounced characteristic is that it specifically is NOT a "legal" limit.

As of 1991, there is no "primary" (enforceable) regulation on silver because it has been deemed to be absolutely not toxic by EPA. Only the "secondary" (unenforceable) guideline exists, as an "advisory" (SMCL).

The DWEL is derived directly from the cosmetic RfD based on an average adult's water consumption. We consider the DWEL useless because it assumes water is the only source of silver, which is not realistic. Lacking any clear explanation to the contrary, we have to assume that the "Longer-Term" (7-year exposure limit) was arbitrarily equated with the DWEL by EPA.

EPA says there are no current "Shorter-Term" exposure limits on silver. The closest thing to short-term limits is what is shown in the "Longer-Term" column on page 9 of DWRHA (page [9] hereof). Thus, we have considerable latitude in recommending increased dosages over short-term use for acute conditions.

Note that the SMCL on page 9 of DWRHA (page [9] hereof) under "Lifetime" matches the figure on page 10 of DWRHA (page [10] hereof) under SMCL. (Dr. Julie Du told us these are the same thing.)

Calculations

- RfD is the recommended limit on total silver intake per day from all sources, measured in micrograms per kilogram of body weight per day: RfD is the Reference Dose commensurate with a lifetime dose over a 70-year period as a Health Advisory (HA) for cosmetic effect only!
    - note: after determining the conservatively safe limit for daily intake, EPA then applies an *additional* Safety Factor of 3 to the RfD, resulting in a greatly reduced limit
- SMCL is the "unenforceable" maximum allowable amount of silver per liter of water, derived directly from the RfD
- DWEL is calculated directly from the RfD, based on average daily water consumption
    - note: we consider the DWEL useless because it assumes the only source of silver is the water
- EPA estimates that a 70-kilogram adult consumes 2 liters of water per day (see HADWC, page 15, line 3 (page [14] hereof)
- EPA cites WHO estimates, which show average daily dietary intake of silver ranges from 20 mcg to 80 mcg per day (0.02 mg to 0.08 mg per day)
- to determine "available" additional room for safe silver intake levels, we total the maximum intake of silver from water per the SMCL, plus the maximum intake of silver from the diet per WHO, and the numbers show that the use of Silver 100™ does not exceed the total RfD when adding all three figures together
    - note: it is *extreme* to assume these maximums for water and diet intake, especially since there is the further Safety Factor of 3 factored into the RfD (see HADWC, page 14, Uncertainty Factor (page [13] hereof)
        - thus, there is a very generous factor of safety built in with the figures we are using for our calculations in determining the safety of our recommended dosages of Silver 100™
- the RfD is 0.005 mg per kg of body weight per day, which is the same as 5 mcg per kg per day
- if you multiply 0.005 mg by 70-kg (the EPA's estimate of the "average" adult's body weight) you get 0.35 mg per day (or 350 mcg per day) for the average (70-kg) adult
- on an average of a 70-year lifetime (at 365.25 days per year), that results in 8.948625 total grams in a lifetime (orally!) as safe for total silver intake without being at risk of argyria; this is a key reference point
- we then refer to the SMCL, which is a maximum (recommended, but "unenforceable") amount of 0.1 mg of silver per liter at an average water consumption for an adult of 2 liters per day, totaling 0.2 mg of silver per day from the water
    - note that we're assuming 0.1 in our math, which exceeds the maximum of the actual range of 0.02 to 0.08 mg per liter per day per EPA worst-case estimates, giving us an additional safety factor built into our calculations

- we then refer to the WHO estimate of a maximum of 0.08 mg (80 mcg) of silver per day from the diet
    - note that we're assuming the maximum of the actual range of 20-80 mcg as per WHO 1984
        - dietary silver content has been consistently going down for decades and is probably less now than in 1984, adding further to our built-in safety factor and contributing substantially to the argument for supplementing silver in our diets
- now, to tally up the totals per a 70-kg adult:
    - RfD minus SMCL minus WHO diet estimate equals the ultra-conservative "available" safe amount for "other" sources of silver
    - RfD is 0.35 mg of silver per day
    - SMCL is 0.2 mg of silver per day (assumes 2 liters of water which is EPA average estimate)
    - WHO dietary silver intake estimate is 0.08 mg of silver per day
    - thus, the math is as follows:
        - 0.35 mg minus 0.2 mg minus 0.08 mg equals 0.07 mg of silver "available" as an ultra-conservative number for safe intake of silver from "other" sources per day
    - relating all this to Silver 100™:
        - our maximum recommended daily dosage is 1 drop per 10 lbs of body weight per day
            - according to the FDA, a drop contains 0.04683 grams of water, which converts to 21.353833 drops per gram (this assumes a cc is equal to a gram of water, which is accurate to within less than two-tenths of one percent at room temperature)
        - a 70-kg adult converts to 154.32 lbs
        - our maximum recommended daily dosage results in 15.432 drops of Silver 100™ being consumed per day for a 70-kg adult
            - divide that 15.432 by the number of drops in a gram, which is 21.353833 drops, and you get 0.72268 grams of Silver 100™ that is being consumed by that 70-kg adult in a day
            - Silver 100™, at 100 ppm, contains 0.1 mg (100 mcg) of silver per gram
            - bottom line: 70-kg adult will be taking in 0.072268 mg of silver per day from Silver 100™, which is virtually identical (within 0.65%) to the ultra-conservative "available" safe amount for "other" sources of silver

If we assumed the maximum worst-case scenario of 0.08 mg/L of silver in drinking water rather than the SMCL of 0.1 mg/L, the math would reveal a remaining amount for silver intake yet "available" after taking Silver 100™ of 37.732 mcg (0.037732 mg) of silver per day (or 52% more Silver 100™ per day).

The above math assumes the worst-case scenarios for silver intake from drinking water and dietary sources, for the percentage of ingested silver that may be retained by the body, and for the total silver required to begin argyria. For this combination of worst-case scenarios to exist together is extraordinarily unlikely, yet even if they did, we still accommodate the Safety Factor of 3 (3 times the dosage is safe).

The following are rules of thumb for performing conversions:

100 ppm = 100 mg/kg = 100 mcg/g = 100 mg/L of water
SMCL = 0.1 mg of silver per liter of water = 0.1 ppm

DRINKING WATER REGULATIONS

AND HEALTH ADVISORIES

by

Office of Water
U.S. Environmental Protection Agency
Washington, D.C.

(these data updated every 6 months
BUT HASN'T BEEN YET!
(PBK 11-30-98)

EPA/822-B-96-002
October 1996

Ohio EPA 8/686-8930 — '97 OHIO TOLD BOB NO STATES ENACTED TIGHTER REGULATIONS
Jeff Stark x6118
Drinking Water Quality

Rec'd 12/11/97 Bill Cook

Recycled/Recyclable
Printed on paper that contains at least 50% recycled fiber.

These regulations and health advisory tables are revised approximately every 6 months by EPA's Office of Water. Although no permanent mailing list is kept, copies may be ordered free of charge from the:

SAFE DRINKING WATER HOTLINE
1-800-426-4791
Monday thru Friday, 9:00 AM to 5:30 PM EST.

Copies of the supportive technical documentation for the health advisories can be obtained for a fee from the:

Educational Resource Information Center (ERIC)
1929 Kenny Road
Columbus, OH 43210-1080
Telephone number (614) 292-6717
FAX (614) 292-0263
e-mail ERICSE@osu.edu
Payment by Purchase Order/check/Visa or Mastercard.

The Health Advisories available and their ERIC order numbers are included at the end of this publication. For further information regarding the Drinking Water Regulations and Health Advisories, call Barbara Corcoran in EPA's Office of Water at (202) 260-1332.

LEGEND

Abbreviations column descriptions are:

MCLG: Maximum Contaminant Level Goal. A non-enforceable concentration of a drinking water contaminant that is protective of adverse human health effects and allows an adequate margin of safety.

MCL: Maximum Contaminant Level. Maximum permissible level of a contaminant in water which is delivered to any user of a public water system.

RfD: Reference Dose. An estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime.

DWEL: Drinking Water Equivalent Level. A lifetime exposure concentration protective of adverse, non-cancer health effects, that assumes all of the exposure to a contaminant is from a drinking water source.

SMCL: Secondary Maximum Contaminant Level = unenforceable

The codes for the **Status Reg** and **Status HA** columns are as follows:

- **F** final
- **D** draft
- **L** listed for regulation
- **P** proposed
- **T** tentative (not officially proposed)

Other codes found in the table include the following:

- **NA** not applicable
- **PS** performance standard 0.5 NTU-1.0 NTU
- **TT** treatment technique

Large discrepancies between Lifetime and Longer-term HA values may occur because of the Agency's conservative policies, especially with regard to carcinogenicity, relative source contribution, and less-than-lifetime exposures in chronic toxicity testing. These factors can result in a cumulative UF (uncertainty factor) of up to 5 to 5000 when calculating a Lifetime HA.

The scheme for categorizing chemicals according to their carcinogenic potential is as follows:*

Group A: **Human carcinogen**	Sufficient evidence in epidemiologic studies to support causal association between exposure and cancer
Group B: **Probable human carcinogen**	Limited evidence in epidemiologic studies (Group B1) and/or sufficient evidence from animal studies (Group B2)
Group C: **Possible human carcinogen**	Limited evidence from animal studies and inadequate or no data in humans
Group D: **Not classifiable**	Inadequate or no human and animal evidence of carcinogenicity
Group E: **No evidence of carcinogenicity for humans**	No evidence of carcinogenicity in at least two adequate animal tests in different species *or* in adequate epidemiologic and animal studies

Drinking Water Health Advisories (HAs) are defined as follows:

One-day HA:	The concentration of a chemical in drinking water that is not expected to cause any adverse noncarcinogenic effects for up to 5 consecutive days of exposure, with a margin of safety.
Ten-day HA:	The concentration of a chemical in drinking water that is not expected to cause any adverse noncarcinogenic effects up to 14 consecutive days of exposure, with a margin of safety.
Long-term HA:	The concentration of a chemical in drinking water that is not expected to cause any adverse noncarcinogenic effects up to approximately 7 years (10% of an individual's lifetime) of exposure, with a margin of safety.
Lifetime HA:	The concentration of a chemical in drinking water that is not expected to cause any adverse noncarcinogenic effects over a lifetime of exposure, with a margin of safety.

*EPA is in the process of revising the Cancer Guidelines.

Drinking Water Standards and Health Advisories

October 1996

BOB GOT THIS DEFINED BY CALLING THE EPA DRINKING WATER HOTLINE?

ASSUMES 2 LITER/DAY (CAN GO UP OR DN W/ WEATHER)

RfD

KICKER: LIFETIME IS IF WATER IS ONLY SILVER SOURCE:

Chemicals	Standards: Status Reg.	Standards: MCLG (mg/l)	Standards: MCL (mg/l)	Status HA	Health Advisories, 10-kg Child: One-day (mg/l)	10-kg Child: Ten-day (mg/l)	10-kg Child: Longer-term (mg/l)	70-kg Adult /154-32lb: Longer-term (mg/l) 7 YRS	70-kg Adult: RfD (mg/kg/day)	70-kg Adult: DWEL (mg/l)	70-kg Adult: Lifetime (mg/l) 70 YRS	70-kg Adult: mg/l at 10^{-4} Cancer Risk	Cancer Group
Nitrite (as N)	F	1	1	F	-	1*	-	-	0.16*	-	SMCL	-	-
Nitrate + Nitrite (both as N)	F	10	10	F	-	-	-	-	-	-	-	-	-
• Selenium	F	0.05	0.05	-	-	-	-	-	0.005	-	-	-	-
⊗ Silver	-	-	-	D	0.2	0.2	0.2	0.2	0.005 +	0.2	0.1 SMCL	-	D
• Sodium	-	-	-	D	-	-	-	-	-	20**	-	-	-
Strontium	L	-	-	D	25	25	25	90	0.6	90	17	-	D
Sulfate	P	500	500	D	-	-	-	-	-	-	-	-	-
Thallium	F	0.0005	0.002	F	0.007	0.007	0.007	0.02	0.00007	0.0023	0.0005	-	-
Vanadium	T	-	-	D	-	-	-	-	-	-	-	-	D
White phosphorous	-	-	-	F	-	-	-	-	0.00002	0.0005	0.0001	-	D
• Zinc	L	-	-	D	6	6	3	10	0.3	10	2	-	D
Zinc chloride (measured as Zinc)	L	-	-	F	6	6	3	10	0.3	10	2	-	D
RADIONUCLIDES													
Beta particle and photon activity (formerly man-made radionuclides)	F	++	4 mrem	-	-	-	-	-	-	-	-	4 mrem/y	A
Gross alpha particle activity	F	++	15 pCi/L	-	-	-	-	-	-	-	-	15 pCi/L	A
Combined Radium 226 & 228	F	++	5 pCi/L	-	-	-	-	-	-	-	-	20 pCi/L	A
Radon*	P	zero	300 pCi/L	-	-	-	-	-	-	-	-	150 pCi/L	A
Uranium*	P	zero	20 µg/L	-	-	-	-	-	0.003	-	-	•	A

* Under review. ** Guidance.

\+ 1991 Proposed National Primary Drinking Water Rule for Radionuclides

++No final MCLG, but zero proposed in 1991.

\+ Cosmetic only for Argyria per Dr Julie Du 12/17/97
@ EPA Hotline (202) 260-7583

(RfD) of .005 mg/Kg/Day @ 70 Kg adult → 8.95 gm Ag in 1 lifetime of 70 yrs
8,948,625
→ .35 mg/day for 70 Kg adult
of which .2 mg may be from 2 liters drinking water → 5.113 gm Ag/70 yr lifetime from drinking H2O
thus @ worst drinking H2O Ag level there remains .15 mg Ag/day as "safe" for 70 Kg Adult

@ Silver 100', 100 PPM = .1 mg / gm
1 gm = 21.353833 drop
@ 1 drop/10 lb @ 70 Kg = 15.4 drop = .0723 mg Ag/day

[9]

Secondary Maximum Contaminant Levels

October 1996

Chemicals	Status	SMCLs (mg/L)
• Aluminum	F	0.05 to 0.2
• Chloride	F	250
Color	F	15 color units
Copper → See "CHEMICALS"	F	1.0
Corrosivity "INORGANICS"	F	non-corrosive
Fluoride* for Action Levels re: Cu & Pb	F	2.0
Foaming agents	F	0.5
• Iron	F	0.3
Manganese	F	0.05
Odor	F	3 threshold odor numbers
• pH	F	6.5 — 8.5
⊙ Silver	F	0.1 ← RfD/Cosmetic Ref. only (argyria)
Sulfate	F	250
Total dissolved solids (TDS)	F	500
Zinc	F	5

Status Codes: P — proposed, F — final

* Under review.

Secondary Drinking Water Standards are unenforceable federal guidelines regarding taste, odor, color and certain other non-aesthetic effects of drinking water. EPA recommends them to the States as reasonable goals, but federal law does not require water systems to comply with them. States may, however, adopt their own enforceable regulations governing these concerns. To be safe, check your State's drinking water rules.

so long as they are at least as stringent.

= 5 µg/Kg Body Wt/day (rounded up from 4.6594)

derived from: 25 gm lifetime / 25,550 Days in 70 yrs [@ 4% max absorption equiv to 1 gm I.V.]

= 978.4736 µg/day "Safe" lifetime dose

Divide by (3) "uncertainty Factor" → 326.16 µg/day for sensitive indiv.

Subtract 80 µg/day in food (Max WHO '84)

Subtract 160 µg/day in water (Max ATSDR 1990 p. 76)

Ag: Max Food/Max Water 86 µg/day w/ at least 4 "Safety" factors

a) 1 → 30 gr. range

a) 4% absorption assumed when range is 1 → 4%

b) Uncertainty factor #3 for sensitive individuals (WHO)

18.36 Days @ 4.6533 µg

c) 80 µg/day in food (WHO '84) when range is 20 → 80 µg/day

d) 160 µg/day in water when range is 40 → 160 µg from ... (ATSDR '90)

"Safety Factors" accruing such that only 86 µg Ag/day (non-food/non-water) is perfectly safe

[10]

Dr. Julie Du

U.S. EPA DW (DRINKING WATER) **SILVER** April 1992

HA, Lewis Publishers 1993

Originally Dec 1990

→ provided to:

"Health Advisories for Drinking Water Contamination" 1993

ISBN 0-87371-931-X

Pages 213 → 238

I. GENERAL INFORMATION AND PROPERTIES

A. CAS No. 7440-22-4

B. Structural Formula

- Not applicable.

C. Synonyms

- Argentum; argentum crede; C•I•77820; collargol; L-3; shell silver; silber (German); silver atom; silver colloidal (Weast, 1977; Stokinger, 1981).

D. Uses

- Silver is used in coinage; the manufacture of tableware, jewelry and ornaments; electroplating; the manufacture of solder, brazing alloys and high-capacity silver-zinc and silver-cadmium batteries; the processing of food and beverages; inks and dyes; etching of ivory and electrical contacts. Silver is also used as a drinking water disinfectant and as a catalyst in hydrogenation and oxidation. It is extensively used in photographic processing, in mirror production and in dental alloys. Silver salts are used in the treatment of warts and burns.

- In addition to metallic silver, compounds of silver used are silver oxide, silver acetate, silver bromide, silver chloride, silver cyanide, silver iodate, silver iodide, silver nitrate and silver sulfate (Stokinger, 1981). The use of dilute silver nitrate solution ($AgNO_3$) for prophylaxis against ophthalmia neonatorum is still a routine requirement in some States (Harvey, 1985). Silver oxide is used in the purification of drinking water because of its toxicity to bacteria and other potentially pathogenic microorganisms (Budavari et al., 1989).

E. Properties (Weast, 1977; Hawley, 1981)

Chemical Formula	Ag
Molecular Weight	107.868
Physical State	Soft, ductile, malleable, lustrous white metal, face-centered cubic structure
Boiling Point	2,212°C
Melting Point	960.5°C
Density	10.50 g/mL at 20°C
Vapor Pressure	—
Water Solubility	Silver is insoluble in water and soluble in fused alkali hydroxides, peroxides and cyanides, hot sulfuric and nitric acids. Most silver salts have limited solubility in water; the solubilities of silver nitrate and

Ref: Dr. Julie Du @ EPA H.Q. (202)260-7583 given was 5 mg each for five treatments and 10 mg each for five more treatments, for a total of 75 mg silver. An inert material was used as the vehicle control, and cadmium was used as a positive control. No fibrosarcomas appeared at the injection site in silver-treated rats. Injection site sarcomas were found only in the vehicle-control (1/50) and cadmium-treated (30/50) rats. The latent period in the vehicle-control group was 19 months, and the latent period in the cadmium-treated group was as short as 4 months. The authors concluded that silver was not tumorigenic when administered as a finely divided powder.

IV. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

A. One-day Health Advisory

No data suitable for determining the One-day Health Advisory (HA) for silver was found in the available literature. Acute toxicity studies such as Dequidt et al. (1974) provide data on lethal doses but do not provide the dose-response data required to calculate the HA. The cosmetic Drinking Water Equivalent Level (DWEL) for silver of 0.2 mg/L calculated below is recommended for use as a conservative estimate of the One-day HA for a child or an adult.

B. Ten-day Health Advisory

No data suitable for determining the Ten-day HA for silver was found in the available literature. Short-term studies have provided information on lethal doses, but have not provided NOAELs or LOAELs. The cosmetic DWEL for silver of 0.2 mg/L calculated below is recommended for use as a conservative estimate of the Ten-day HA for a child or adult.

C. Longer-term Health Advisory

No data suitable for determining the Longer-term HA for silver were found in the available literature. The data found were not sufficient to establish a NOAEL and LOAEL. The cosmetic DWEL for silver of 0.2 mg/L calculated below is recommended as a conservative estimate of the Longer-term HA for an adult or a child.

D. Lifetime Health Advisory

Specific information on adverse health effects in humans or animals of oral exposure to graded levels of silver needed for setting Lifetime Health Advisory levels, was not found in the available literature. Two reports of argyria following ingestion of silver were found (Blumberg and Carey, 1934; East et al., 1980), but these reports are of single cases with inadequate documentation of the dose rate. On the other hand, valuable clinical and therapeutic data were presented on human cases of argyria by Gaul and Staud (1935, as cited in U.S. EPA, 1980) and by Hill and Pillsbury (1939, as cited in U.S. EPA, 1980). These data indicate that about 0.9 to 1.5 g of silver administered over a period of 1 to 2 years as iv injections will cause argyria in patients. However, the individuals are likely to have been sensitive because they were in the late stages of syphilis. Furthermore, many other patients received similar dose regimen without developing argyria.

→ 1 gram does it w/ I.V. but DWSHA shows 8.95 as RFD with what is implicitly ORAL dosage

E. Derivation of the Lifetime Health Advisory for the Cosmetic Effect of Silver

A Lifetime HA based on cosmetic effects is calculated assuming that 1 g of iv silver will produce mild argyria in the most sensitive individuals (Gaul and Staud, 1935; Hill and Pillsbury, 1939). Assuming a 4% absorption rate (Furchner et al., 1968) following oral exposure, the 1-g iv dose corresponds to an oral dose of 25 g (1 g/ 0.04 = 25 g). This dose is then averaged over a lifetime, assumed to be 70 years:

$$\frac{70 \text{ years}}{= 25{,}550 \text{ days @ 365 (not 365.25) days/year}} \times 25 \text{ g} = \overbrace{978 \ \mu\text{g/day}}^{978.47358}$$

Based on an adult body weight of 70 kg, this corresponds to the Lowest-Observed-Cosmetic-Effect Level of 14 μg/kg/day (978 μg/day/70 kg = 14 μg/kg/day). Using 14 μg/kg/day as the Lowest-Observed-Cosmetic-Effect level for silver, a Lifetime HA for the cosmetic effect of silver is calculated as follows:

Step 1: Determination of the Cosmetic RfD

RfD IS: 5 MCG/KG/DY

$$\text{Cosmetic RfD} = \frac{\overbrace{14 \ \mu\text{g/kg/day}}^{13.978194}}{3} = \overbrace{4.7}^{4.6594} \ \mu\text{g/kg/day (rounded to 5 } \mu\text{g/kg/day)}$$

where:

14 μg/kg/day = Lowest-Observed-Cosmetic-Effect Level based on argyria.

3 = Uncertainty factor: An uncertainty factor of 3 is used to estimate an RfD associated with lifetime exposure. This uncertainty factor was applied for the following reasons: First, a 10-fold uncertainty factor is usually applied to human data to account for intraspecies variability. However, since this calculation has already included sensitive individuals, a 10-fold uncertainty factor is not warranted. Second, an uncertainty factor less than 10 (i.e., 3) is sufficiently protective since the estimated dose causing argyria within 1-3 years is being apportioned over a lifetime, and the effect is based on argyria which is considered a cosmetic effect, and not an adverse health effect.

Step 2: Determination of the Cosmetic DWEL: *

$$\text{Cosmetic DWEL} = \frac{5 \ \mu\text{g/kg/day} \times 70 \text{ kg}}{2 \text{ L/day}} = \overbrace{175 \ \mu\text{g/L}}^{163.079} \text{ (rounded to } \overset{?}{200} \ \mu\text{g/L)}$$

* Reflected in SMCL (Secondary Maximum Contaminant Level)** in EPA Office of Water's "Drinking Water Regulations & Health Advisories" Oct '96 EPA 822-B-96-002 (14)

** SMCL is a guideline only; not enforceable; Silver SMCL Cosmetic Only.

where:

5 µg/kg/day	=	cosmetic RfD.
70 kg	=	assumed weight of an adult.
2 L/day	=	assumed water consumption of a 70-kg adult.

The DWEL is derived on the assumption that 100% of the silver intake comes from drinking water. As estimated by the World Health Organization (WHO, 1984), the upper-bound intake of silver from food is 20 to 80 µg/day and is essentially negligible from air. Therefore, the Lifetime HA for the cosmetic effect of silver can be calculated by subtracting the amount of silver obtained in food. DIET!

Step 3: Lifetime HA for the Cosmetic Effect of Silver

in drinking water

Lifetime HA for Cosmetic Effect =

*350 µg/day = RfD; Food Value = 80 µg/day

$$\frac{(0.005\ \text{mg/kg/day})\ (70\ \text{kg}) - 0.08\ \text{mg/day}}{2\ \text{L/day}} = 0.135\ \text{mg/L (rounded to 0.1 mg/L)}$$

(Adult Water Intake) "Normalized"

ie 100 µg/L = new SMCL for Silver 12/90 previous value was 50 µg/L

* actually: 326.158 µg/day using 4.6594 µg/kg/day

** actually: 123.079 µg/L

Thus, a concentration of silver in water of 100 µg/L or 0.1 mg/L is considered protective of the cosmetic effect of silver (argyria) for the general population.

F. Evaluation of Carcinogenic Potential

Applying the criteria described in the U.S. EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), silver has been classified in Group D: not classified. This category is for agents with inadequate animal evidence of carcinogenicity.

V. OTHER CRITERIA, GUIDANCE AND STANDARDS

MAXIMUM CONTAMINATION LEVEL (ENFORCEABLE)

KEY IT!

- The U.S. EPA had originally regulated silver with an MCL of 50 µg/L. However, since silver caused only argyria, a cosmetic effect, the U.S. EPA (1991) replaced the primary (= Enforceable) standard of 50 µg/L with a value of 100 µg/L as the secondary standard.

= SMCL → UNENFORCEABLE FEDERAL "GUIDELINE" (SEE ¶ @ BOT OF PG 10 OF DWRHA)

VI. ANALYTICAL METHODS

- Most of the methods available for silver analysis involve atomic absorption spectroscopy. In these methods, the metal is dissolved and thermally excited. When excited, the metal absorbs light frequencies characteristic of that element. In addition, colorimetric (dithizone) methods (American Public Health Association, 1976) and inductively coupled plasma atomic emission spectroscopy can be used to analyze silver (CFR, 1987)

ATSDR

Crucial Pages Excerpted from

FAX

Agency for Toxic Substances and Disease Registry

[TP-90-24] Dec. 1990 Toxicological Profile for Silver

Addressee: Bob Tuck

Addressee Telephone Number:

Facsimile Telephone Number:

Sender:

Mike Fay, Ph.D.
ATSDR, Div. of Toxicology
1600 Clifton Rd., MS E-29
Atlanta GA 30333

Sender Telephone Number: 404-639-~~6308~~ 5289

Number of Pages: 9 (including this page)

Date: 12/12/97

Subject: Pages from Tox Profile for Silver

Comments:

ATSDR FACSIMILE TRANSMISSION NUMBERS:

Office of the Assistant Administrator
Executive Park, Building 37, Room 3726
639-0700; Fax # 639-0744

Office of the Associate Administrator for Science
Executive Park, Building 37, Room 3720
639-0708; Fax # 639-0586

ATSDR Washington Office
Hubert H. Humphery Building, Washington, DC
202-472-7136; Fax # 202-690-6985

Office of Federal Programs
Executive Park, Building 37, Room 3756
639-0730; Fax # 639-0744

Office of Information Resources Management
Executive Park, Building 37, Room 3733
639-0720; Fax # 639-0740

Office of Policy and External Affairs
Executive Park, Building 37, Room 3735
639-0727; Fax # 639-0715

Office of Program Operations and Management
Executive Park, Building 35, Room 3526
639-0550; Fax # 639-0560

Office of Regional Operations
Executive Park, Building 37, Room 3701
639-0707; Fax # 639-0713

Regional Fax Numbers

Region 1:	617-860-4397	Region 6:	214-655-2237
Region 2:	212-264-9674	Region 7:	913-551-7063
Region 3:	215-597-0994	Region 8:	303-294-7559
Region 4:	404-347-1667	Region 9:	415-744-1796
Region 5:	312-353-9354	Region 10:	206-553-2142

Division of Health Assessment and Consultation
Executive Park, Building 31, Room 3134
639-0610; Fax# 639-0654

Division of Health Education
Executive Park, Building 4, Room 1104
639-6204; Fax # 639-6207/6208

Division of Health Studies
Executive Park, Building 4, Room 1117
639-6200; Fax # 639-6220

Division of Toxicology
Executive Park, Building 4, Room 2449
639-6300; Fax # 639-6315

(404) area code
Atlanta, Georgia

11/18/97 Jay: I have also included the entire [TP-90-24]

4-92

Rec'd 12/14/97
[signature]

Hem (1970) reported a median silver concentration of 0.23 μg/L in U.S. drinking water. Letkiewicz et al. (1984) analyzed the results of three surveys of U.S. groundwater and surface water used as drinking water supplies. These surveys were the 1969 U.S. Public Health Service Community Water Supply Survey (CWSS 1969), the 1978 EPA Community Water Supply Survey (CWSS 1978), and the 1978 through 1980 EPA Rural Water Survey (RWS). In CWSS 1969, silver was detected (minimum positive value was 0.1 μg/L) in 309 of 677 groundwater supplies, (mean 1.7 μg/L, median 1.3 μg/L, and range 0.1 to 9 μg/L). Silver was detected in 59 of 109 surface water supplies with a mean and median of 1.3 μg/L and a range of 0.1 to 4 μg/L. In CWSS 1978, silver was detected (minimum positive value was 30 μg/L) in 8 of 81 groundwater supplies (range 30-40 μg/L, mean 31.9 μg/L, and median 30 μg/L). Silver was found in 4 of 25 surface water supplies (range 30-40 μg/L, mean 36.2 μg/L, and median 37.5 μg/L). In the RWS* conducted between 1978 and 1980, silver was detected (minimum quantifiable concentration apparently was 20 μg/L) in 10 of 71 groundwater supplies (mean and median 40 μg/L and range 20-80 μg/L). Silver was detected in 8 of 21 surface water supplies. The range, mean, and median of these 8 supplies were 20-60 μg/L, 36.2 μg/L, and 35 μg/L, respectively. Letkiewicz et al. (1984) also summarized information from EPA's Federal Reporting Data System as of 1984, which indicated that 14 public water supplies (13 from groundwater) in the United States reported silver levels above 50 μg/L. Letkiewicz et al. (1984) stated that it is not possible to determine which of these surveys is representative of current levels of silver in the U.S. water supply. The large range in apparent detection limits further limits the usefulness of these data in estimating silver levels in U.S. water supplies.

* Cinti Ag claims a detection limit = .0003 = .3 μg/L

Max. Conc. of 80 μg/L for Silver in drink water!

Silver has been detected with a geometric mean concentration of 6.0 μg/L in groundwater samples from 613 of the 2,783 (22%) hazardous waste sites included in EPA's Contract Laboratory Program (CLP) statistical database (CLP 1988). It has also been detected in surface water samples from 552 of the 2,783 (20%) sites in the CLP statistical database with a geometric mean concentration of 9.0 μg/L (CLP 1988).

5.4.3 Soil

From a series of measurements in Canada, Boyle (1968) estimated that the average silver content of soils (except for mineralized zones such as mining areas) was 0.30 ppm and the average abundance in the earth's crust was 0.10 ppm. The major source of elevated silver levels in cultivated soils is from the application of sewage sludge and sludge effluents (Smith and Carson 1977). The average silver concentration in soils near a lead smelting complex in Kellogg, Idaho (in the Coeur d'Alene River Basin) was 20 ppm (range: 3.2-31 ppm) (Ragaini et al. 1977). Klein (1972) measured soil metal concentrations in the Grand Rapids, Michigan area in order to examine possible relationships between concentrations and land use. Silver concentrations in soils that were classified by land use were 0.13 ppm (residential), 0.19 ppm (agricultural), and 0.37 ppm (industrial) (Klein 1972).

* RWS = Rural Water Survey

The Contract Laboratory Program (CLP) statistical database indicates that silver has been detected with a geometric mean concentration of 4.5 ppm in soil samples from 1,807 of 2,783 (65%) hazardous waste sites that have had samples analyzed by the CLP (CLP 1988).

5.4.4 Other Media

Coal has been reported to contain silver at concentrations of up to 10 ppm (Boyle 1968). Klusek et al. (1983) measured the following silver concentrations at a bituminous coal-fired electric generating station: coal -- 0.29 mg/kg; fly ash -- 1.6 mg/kg; and bottom ash -- <0.1 mg/kg. In the combustible portions of municipal solid waste, mean silver concentrations were 3 ppm (range: <3-7 ppm) (Law and Gordon 1979). A municipal incinerator was found to emit particles containing 390 ppm silver (Law and Gordon 1979). The mean and maximum silver concentrations in U.S. sewage sludge were 225 mg/kg ? and 960 mg/kg (dry weight), respectively (Bunch 1982). Sludge silver concentrations (mg/kg dry weight) were reported as follows: from sewage treatment plants with industrial or municipal wastes -- 15-120 mg/kg; from plants with photoprocessing effluents as a source -- 450-27,000 mg/kg (Lytle 1984). !

before Treatment? ? refine and cash in! *

Scow et al. (1981) reported that the median silver concentrations in sewage treatment plant influent and effluent were 0.008 mg/L and 0.002 mg/L, respectively. Treated effluents from a large photographic processing plant contained an average of 0.07 mg/L silver (range: <0.02-0.30 mg/L) in the form of silver thiosulfate complexes, silver bromide, and silver sulfide (Bard et al. 1976). !

* ? 70 PPB vs 27,000 PPM?

Cunningham and Stroube (1987) collected samples of various foods in 20 U.S. cities between 1979 and 1980. Silver concentrations (mg/kg wet weight) in composite samples of the following food groups were: dairy products -- <0.061; meat, fish, and poultry -- mean 0.015, range 0-87; cereal and grain products -- mean 0.008, range 0-0.140; leafy vegetables -- mean 0.007, range 0-0.039; fruits -- <0.050; oils and fats -- <0.030. The average silver concentration of a mixture of 201 foods prepared to represent the typical U.S. diet was 0.0091 mg/kg dry weight (Iyengar et al. 1987). The average concentration in cow's milk in the United States has been reported to be 0.047 ppm (range:0.037-0.059 ppm) (Murthy and Rhea 1968). EPA (1980a) summarized data on silver content in food as follows: beef -- 0.004-0.024 mg/kg; pork -- 0.007-0.012 mg/kg; mutton and lamb -- 0.006-0.011 mg/kg; tea -- 0.20-2.00 mg/kg (dry weight); mollusks -- 0.1-10.0 mg/kg.

** 9.1 µg/kg 4.5 µg/day from food (same source pg 78) ∴ Food intake est 2 @ 1/2 kg

Mean silver concentrations in one brand of nonfilter and filter cigarettes were reported to be 0.18 mg/kg and 0.27 mg/kg, respectively (Nadkarni et al. 1970).

In a summary of 1975-1979 data on fish tissue from EPA's STORET database, the mean concentration of silver in 221 samples was 0.225 mg/kg (wet weight

ATSDR = Agency for Toxic Substances & Disease Registry
"Toxicological Profile for Silver" 1990
ATSDR TP-90-24

These pages from:

Ref: Silver 100 @ 100 PPM
ie → 100 μg/ml
@ 100 mg/liter
ie → 100,000 μg/liter
= 100,000,000 ng/liter!

total fish), with a range of 0.004-1.900 mg/kg (Scow et al. 1981). In Lake Pontchartrain, Louisiana (which is likely to receive substantial inputs of metals from municipal and agricultural activities) silver concentrations in clams and American oyster tissues were 0.4-2.4 mg/kg and 5.5 mg/kg (all dry weight), respectively (Byrne and DeLeon 1986).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Food and water are the most likely major sources of exposure to natural and anthropogenic silver for the general U.S. population (Letkiewicz et al. 1984). The general population is also exposed through the inhalation of airborne silver and the dental and medical uses of silver. Letkiewicz et al. (1984) estimated that about 50% of the 214 million people in the United States who use public drinking water supplies had silver present in their water at 0.01-10 μg/L; 10-30% may receive water with levels greater than 30 μg/L. They estimated that 46,000 people in the U.S. receive drinking water with silver concentrations exceeding the current U.S. Safe Drinking Water Act maximum contaminant limit of 50 μg/L. Swimming pool water purified with silver-containing systems is another possible source of exposure to silver.

? vs .1 PPM = .1 mg/L
SMCL (Secondary Max. Contam. Level) = 100 μg/L

The averaged daily dietary intake (including fluids) of silver has been estimated to be 70 μg/day (Snyder et al. 1975) and 88 μg/day (Kehoe et al. 1940). The average daily dietary intake of two subjects over 30 days was determined to be 35-44 μg/day (Tipton et al. 1966). The silver content of food was estimated at 4.5 μg/day based on the content of a mixture of 201 foods prepared to represent the typical U.S. diet (Iyengar et al. 1987). Most of the U.S. population breathes air containing a maximum of 1.0 ng/m^3 silver, which contributes a maximum of 0.023 μg/day. Drinking water supplies containing 10 μg/L would provide an estimated 20 μg/day of the 70-88 μg/day estimated daily intake. At levels of 30-50 μg/L, drinking water contributes 60-100 μg/day (based on an estimated daily water intake of 2 L) and constitutes the major source of silver intake (Letkiewicz et al. 1984). Although silver has been detected in cigarettes, the average daily intake from smoking has not been determined. A very limited use of silver salts is in purification systems in isolated locations (such as mountain cabins and in space missions) (Silver Institute 1975).

** See p 77 derived for 1/2 kg food per day @ 9. μg/kg food

The 1972-1974 National Occupational Hazard Survey (NOHS), conducted by NIOSH estimated that 19,343 workers in 2,163 plants were potentially exposed to silver in 1970 (NIOSH 1976). The largest number of exposed workers were in special trade contracting, primary metal industries, and industries using electrical machinery and electrical equipment and supplies. The occupational groups with the largest number of exposed workers were air conditioning, heating and refrigeration mechanics and repairmen; plumbers and pipefitters; miscellaneous assemblers; welders and flamecutters; and miscellaneous machine operators.

plus Ch. 1 Profile page where 50 μg/L is called out as US Max. See p 76

Safe Drinking Water Hotline 8/426-4791 Carol Gray

"Silver Specialist" = Dr. Julie Du (202) 260-7583
@ EPA Headquarters in D.C.
"Locator #(202) 260-2090

@ ATSDR in Atlanta
Mike Fay PhD
x 5289
8/447-1544

Preliminary data from a second workplace survey, the 1980-1983 National Occupational Exposure Survey (NOES) conducted by NIOSH, indicated that 67,054 workers, including 15,763 women, in 3,123 plants were potentially exposed to silver in the workplace in 1980 (NIOSH 1984a). These estimates were derived from observations of the actual use of silver (67% of total estimate) and the use of trade name products known to contain the compound (33%). The largest number of workers were exposed in the primary metal industries, business services, health services, instruments and related products industries, and fabricated metal products industries.

Neither the NOHS nor the NOES databases contain information on the frequency, concentration, or duration of exposure of workers to any of the chemicals listed therein. These surveys provide only estimates of the number of workers potentially exposed to chemicals in the workplace.

Additional industrial processes which act as potential sources of occupational exposure to silver include the processing of silver chemicals such as silver nitrate and silver oxide for uses such as photography, and smelting and refining of silver-containing ores (DiVincenzo et al. 1985).

revealation of assumption 2L/day.

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

The most likely sources of higher than background levels of silver for the general population are ingestion of contaminated food and drinking water. The estimated 46,000 persons in the United States whose drinking water contains more than 50 µg/L silver (attributable to natural and/or anthropogenic sources) would have an estimated daily intake of at least 100 µg/day from water alone (Letkiewicz et al. 1984). Higher levels of silver have been detected in shellfish near industrial or sewage inputs (Byrne and DeLeon 1986; Pesch et al. 1977; Thomson et al. 1984) and are likely to occur in crops grown on sludge-amended soils, in the vicinity of smelters or mining operations, or in areas with naturally high background silver levels.

SMCL now 100 µg/L → 200 µg/day "max" for drinking H2O @ 2 L/day per person

Elevated atmospheric silver concentrations have been attributed to smelting and refining of silver and other metals, and the use of silver iodide in cloud seeding (Scow et al. 1981). Populations living close to mines may have higher exposures. Approximately 71% of domestic mine production occurs in Idaho, Arizona, and Colorado; the Coeur d'Alene River Basin in Idaho supplies the greatest amount of silver (Drake 1980). Crops grown on soils with elevated silver concentrations (either from anthropogenic sources or from naturally high background levels) or exposed to high ambient atmospheric concentrations are likely to become enriched with silver (Ragaini et al. 1977; Ward et al. 1979).

Silver has been used in lozenges and chewing gums designed to aid the cessation of smoking. Silver acetate in chewing gum has been classified as an over-the-counter smoking deterrent by the Food and Drug Administration (Malcolm et al. 1986). Several cases of high body levels of silver have been

INTEGRATED RISK INFORMATION SYSTEM.

"SUMMARY REVIEW"
("WITHOUT REGULATORY IMPACT")

Silver

CHEMICAL ABSTRACTS SERVICE REGISTRY NUMBER (FOR SILVER; NEVER CHANGES) — CASRN 7440-22-4

(03/01/97)

PUT OUT BY THE "AMERICAN CHEMICAL SOCIETY"

Contents

0099
Silver; CASRN 7440-22-4 (03/01/97)

Health assessment information on a chemical substance is included in IRIS only after a comprehensive review of chronic toxicity data by U.S. EPA health scientists from several Program Offices and the Office of Research and Development. The summaries presented in Sections I and II represent a consensus reached in the review process. Background information and explanations of the methods used to derive the values given in IRIS are provided in the Background Documents.

STATUS OF DATA FOR Silver

File On-Line 01/31/87

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	12/01/96
Inhalation RfC Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	06/01/89

---

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 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
Data Base -- 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.