Introduction to Metal Toxicology

GENERAL BACKGROUND RELEVANT TO SILVER - It has finally become recognized that when addressing metal toxicity concerns such as silver or silver compounds, it is the type (speciation) of metal compound or formulation that is all-important. There are no toxicity studies reporting adverse events with silver (i.e., argyria) that were focused exclusively on pure silver. Silver as it occurs in compounds, appears to be the source of all reports on silver’s possible toxicity to higher life forms.¹,²,³

SPECIATION PERTAINING TO SILVER - Speciation is a term that describes the physical and chemical properties of a metal as it relates to the metal’s fate, transport and toxicity. Weakly absorbed metals and metals associated with insoluble sulfides vary greatly in concerns of toxicity.⁴ As regards pure silver or silver compounds intended for ingestion or human exposure, we cite that ATSDR CAS # 7440-22-4 has found no chemicals (food or drug based), which might significantly escalate silver’s toxicity as it relates to silver speciation. Exceptions would be of course certain silver compounds as referenced above.

PERSPECTIVES ON BENEFIT VS TOXICITY AS IT PERTAINS TO NANOSCALAR OR SUB-NANOSCALAR SILVER SPECIATION - The speciation of silver is finally gaining a wider understanding among medical toxicologists, environmental ecologists, and food scientists. Silver speciation is of paramount importance when discussing both the benefits and the toxicities of silver-based drugs. In most every case, the benefits are determined by (a) the silver speciation content of oligodynamic silver ions, yet the toxicity of silver relates to (b) the non-oligodynamic silver content plus (c) the specific anion attached.

Furthermore, it is crucial to differentiate silver speciation even as this pertains to the category of colloidal silver preparations in general. Within this category are speciations of silver hydrosols, typically in the particle size ranges that are either nanoscalar (25 nm – 1 nm) or sub-nanoscalar (< 1 nm). If the manufacturing process excludes contaminants, this speciation represents not only the purest silver therapeutic agents ever created, but inherently the most powerful. Therapeusis will differ by

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orders of magnitude from the larger size particles to the smaller size particles, increasing as the silver particle size decreases. Therapeusis will again be boosted by several orders of magnitude according to what percentage of the silver particles are in the charged state. The higher percentage of charged particles per volume, the greater the microcidal activity. Charged silver particles are by definition “oligodynamic” silver particles. Since pure silver has no known toxicity, such speciations of silver hydrosols possesses a high margin of safety, perhaps greater than any other antimicrobial agent yet discovered.

For reference, when generally discussing the purest high quality silver hydrosols, the acronym OSH will be used to indicate oligodynamic silver hydrosols. More specifically, when discussing nanoscalar oligodynamic silver hydrosols, the acronym NOSH will be used. And when discussing sub-nanoscalar (picoscalar) oligodynamic silver hydrosols, the terms POSH will be used. And finally, when discussing nanotech silver rendered into particle size ranges that remain uniform throughout the product, the term “uniform” will be used. For example, it is possible that a silver hydrosol may possess both nanoscalar and sub-nanoscalar silver particles.

**Historical Authoritative Safety Data**

**OFFICIAL DESIGNATION OR EXCLUSION - UNOFFICIAL DESIGNATION - CRITERIA** - In the early U.S. official monographs, all patented silver preparations were excluded due to the rules of inclusion. Thus, all patented silver drugs were only listed in the N.N.R. or as unofficial in the official monograph compendiums. For example, more than 96 different silver preparations, many used intravenously, were in use prior to 1939, as documented by The Council on Pharmacy and Chemistry of the American Medical Association, yet only 5 official monographs were cited at that time. This historical fact remained until 1975, when all other silver-based drug speciations were dropped with the exceptions of only two silver salts (i.e., silver nitrate and silver sulfadiazine). A very limited number of these pre-1975 silver preparations were silver hydrosols, presently the classification pertaining to the case in concern here (i.e., 22.5 ppm silver 23). However, the classification of silver hydrosols that were comprised exclusively of pure silver and water - and nothing else - was usually not given any recognition or even listed at all. Yet, this speciation of silver was among the first to be discovered and created by Carey Lea in 1891.

**MONOGRAPH SOURCES** - There are in existence many speciations of silver-based drugs that have been listed in Official and Unofficial Pharmacopeial Monographs. Generally these fall under two distinct speciation categories listed in drug compendiums, including:

- The Dispensatory of The United States of America (U.S.D.),
- The British Pharmacopoeia (B.P.),
- The United States Pharmacopoeia (U.S.P.),
- The National Formulary (N.F.), and
- The New and Non-Official Drug Registry (N.N.R.), and in
- Other compilations made by The Council on Pharmacy and Chemistry of the American Medical Association.

**MONOGRAPH DELINEATIONS** – There are clearly two distinct silver speciation categories: (1) silver salts and compounds which form true silver solutions, and (2) colloidal silver which are comprised of insoluble silver particles suspended in water with or without other colloids or electrolytes, making for a total of six separate colloidal silver speciations.

**CATEGORY 1:**
The former silver-based drug speciations officially include:

- Silver nitrate in its various formulations (Argenti Nitras, USP and Argenti Nitras Induratus, USP),\(^{18}\)
- Silver sulfadiazine;\(^{19}\)

Unofficial silver-based drug speciations prior to 1975 included:

- Silver lactate,
- Silver arsphenamine,
- Silver picrate, and
- Silver covalently bound to organic acids such as citrate,
- Silver hexamethylenetetramine,
- Silver methylene blue,
- Silver orthophosphate,
- Silver potassium cyanide,
- Silver sodium thiosulfate,
- Silver thriohydrocarburo-sulfonate,
- Silver phenolsulfonate, and
- Silver picrate.

CATEGORY 2:
The later colloidal silver-based drug speciations prior to 1975 were officially comprised of:

- (1-A) Strong silver proteinates (Argentum Proteinicum Forte, USP), and
- (1-B) Mild silver proteinates (Argentum Proteinicum Mite, USP);

Unofficial colloidal silver-based drug speciations prior to 1965 included:

- (2) Silver proteinates combined with silver salts
- (3) Silver nucleates,
- (4) Silver halides,
- (5) Silver oxides, and
- (6) Silver hydrosols.

Select Quotes From the Authoritative Texts on Silver Hydrosols

“Electrargol is marketed only in solution either in bottles or in sealed tubes. The dose in eighty to one hundred and sixty minims (5-10 cc.) injected intramuscularly or directly into a vein.”

“Electrargol: electric colloidal silver, marketed in the form of a very dilute (0.04 per cent) solution.”\(^{20}\)

“Collosol Argentum. (A.K.A. Collsargen) - A colloidal suspension asserted to contain 0.05% per cent. of metallic silver. It is used in both local and systemic infections. For local use it may be used diluted with 2 parts of water or full strength. For injections in systemic infections the recommended dose is 30 minims (2 cc.). There are available also an ointment and a paste for use in dermatologic conditions.”
For practical discussions keep in mind that the beneficial or biologically meaningful pharmacodynamic characteristics of these silver-based drugs all relate to their oligodynamic action of the silver cations, whether colloidal in speciation or not. In the main, any anion (attached molecule) present defeats the therapeusis of the drug because it dramatically adds to its toxicity. Partial exceptions would include some silver halides (AgI and AgCl), oxides of silver, and silver sulfadiazine, which have added actions contributed by their respective anions. However, with the possible exception of the silver oxides, these anions present increased toxicity issues for the drug. As Goetz stated: “The practical advantage of the electrolytic method of charging water metal lies, or course, in the ability to produce very concentrated solutions (of Ag+) without the presence of high concentrations of anion which, particularly in the case of silver, could be deleterious when used for disinfection…”

**Present Day Safety Data**

   a. Section 4-27; Properties of the Elements and Inorganic Compounds
      i. “While silver itself is not considered toxic, most of its salts are poisonous.”
      ii. “Silver has germicidal effects and kills many lower organisms effectively without harm to higher animals.”

   a. “Based on the current Rfd, for a 5 kg infant to a 70 kg adult, the maximal daily silver exposure should be less than 25-350 µg/d.”
   b. “However, a regular daily diet may contain up to about 90 µg of silver as a background level exposure.”
   c. “Some researchers have suggested that Vitamin E or selenium deficiency may increase susceptibility to systemic silver toxicity. Wagner et al. and Bunyan et al. have shown that hepatic necrosis can be induced by administering silver preparations to Vitamin E/selenium deficient rats. They hypothesized that toxicity was due to a silver-induced selenium deficiency that inhibits the synthesis of the seleno-enzyme glutathione peroxidase. Further, Bunyan et al. showed that if rat diets were supplemented with selenium or Vitamin E, exposure to silver as high as 140 mg/kg/d was still well tolerated.”

3. **e-Medicine Journal, November 2, 2001; Number 11**
   a. “Argyria results from prolonged contact to or ingestion of silver salts. It produces a gray to gray-black staining of skin and mucous membranes produced by silver deposition. Silver may be deposited in the skin either from industrial exposure or as a result of medications containing silver salts.”

a. 1.4 No studies of cancer or birth defects in animals from eating, drinking, or breathing in silver compounds were found. Therefore, it is not known if these effects would occur in humans. One study of animals drinking silver compounds mixed with water for most of their life found no effect on fertility. Another study found reproductive tissues were damaged in animals after they received injections of silver nitrate. However, the tissues recovered even while the animals received more injections of silver nitrate. Tests in animals show that silver compounds are likely to be life threatening for humans only when large amounts (that is, grams) are swallowed and that skin contact with silver compounds is very unlikely to be life threatening.

b. 1.5 Studies in rats show that drinking water containing very large amounts of silver (2589 parts of silver per million parts water, or about 2.6 grams per liter) is likely to be life threatening.

d. 2.2.1. **Inhalation Exposure:**

2.2.1.1. **Death** – No studies were located regarding death in humans or animals after inhalation exposure to silver or silver compounds.

2.2.1.2. **Systemic Effects** – No studies were located regarding cardiovascular or musculoskeletal effects in humans or animals after inhalation exposure to silver or silver compounds.

**Respiratory Effects** – Occupational exposure to silver dusts can also lead to respiratory irritation (Rosenman et al. 1979, 1987).

**Gastrointestinal Effects** – Abdominal pain has also been reported by workers exposed to silver nitrate and oxide in the workplace (Rosenman et al. 1979).

**Hematological Effects** – Blood counts were reported to be normal in all individuals observed in the occupational study of silver-exposed workers conducted by Rosenman et al. (1979) with the exception of one individual with an elevated hemoglobin level.

**Hepatic Effects** – A study that measured levels of several liver enzymes (alanine transferase, aspartate amino transferase, gamma glutamyl transferase, and alkaline phosphatase) found no significant differences between workers exposed to silver and insoluble silver compounds and those with no history of silver exposure (Pifer et al. 1989).

**Renal Effects** – Studies in animals have focused only on the deposition of silver in the kidney following oral exposure (Olcott 1947, 1948) and renal tests were not conducted.

**Dermal/Ocular Effects** – Skin and ocular burns, caused by contact with silver nitrate, have been reported in workers (Moss et al. 1979, Rosenman et al. 1979).

2.2.1.3. **Immunological Effects** – No studies were located regarding immunological effects in humans or animals after inhalation exposure to silver or silver compounds.
2.2.1.4. **Neurological Effects** - No studies were located regarding neurological effects in humans or animals after inhalation exposure to silver or silver compounds.

2.2.1.5. **Developmental Effects** - No studies were located regarding developmental effects in humans or animals after inhalation exposure to silver or silver compounds.

2.2.1.6. **Reproductive Effects** - No studies were located regarding reproductive effects in humans or animals after inhalation exposure to silver or silver compounds.

2.2.1.7. **Genotoxic Effects** - No studies were located regarding genotoxic effects in humans or animals after inhalation exposure to silver or silver compounds.

2.2.1.8. **Cancer Effects** - No studies were located regarding cancer effects in humans or animals after inhalation exposure to silver or silver compounds.

e. 2.2.2. **Oral Exposure**

2.2.2.1. **Death** – No studies located regarding death in humans following oral exposure to silver or silver compounds.

2.2.2.2. **Systemic Effects** – No studies located regarding respiratory, gastrointestinal, hematological, musculoskeletal, hepatic, or renal effects in humans or animals after oral exposure to silver or silver compounds.

2.2.2.3. **Cardiovascular Effects** – No studies were located regarding cardiovascular effects in humans following oral exposure to silver or silver compounds.

2.2.2.4. **Dermal/Ocular Effects** – Gray or blue-gray discoloration of the skin has been observed in individuals that have ingested both metallic silver and silver compounds in small doses over periods of months to years.

2.2.2.5. **Immunological Effects** - No studies were located regarding immunological effects in humans following oral exposure to silver or silver compounds.

2.2.2.6. **Neurological Effects** – Several reports describe the deposition of what are assumed to be silver containing granules in tissue of the central nervous system.

2.2.2.7. **Developmental Effects** - No studies were located regarding developmental effects in humans after oral exposure to silver or silver compounds.

2.2.2.8. **Reproductive Effects** - No studies were located regarding reproductive effects in humans after oral exposure to silver or silver compounds.

2.2.2.9. **Genotoxic Effects** - No studies were located regarding genotoxic effects in humans after oral exposure to silver or silver compounds.

2.2.2.10. **Cancer** - No studies were located regarding cancer effects in humans after oral exposure to silver or silver compounds.

e. 2.2.3. **Dermal Exposure**

2.2.3.1. **Death** - No studies were located regarding death in humans following dermal exposure to silver or silver compounds.
2.2.3.2. **Systemic Effects** – No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, or ocular effects in humans or animals after dermal exposure to silver or silver compounds.

**Dermal** – Medical case histories indicate that dermal exposure to silver or silver compounds for extended periods of time can lead to local skin discoloration similar in nature to the generalized pigmentation seen after repeated oral exposure. However, the amount of silver and the duration of time required to produce this effect cannot be established with the existing information (Buckley 1963; McMahon and Bergfeld 1983).

2.2.3.3. **Immunological Effects** – Medical case histories describe mild allergic responses attributed to repeated contact with silver and silver compounds (Catsakis and Sulica 1978; Heyl 1979; Marks 1966). Sensitization occurred in response to contact with powdered silver cyanide, radiographic processing solutions, and apparently to silver in dental amalgam.

No studies were located regarding the following health effects in humans and animals after dermal exposure to silver and silver compounds.

2.2.3.4 Neurological Effects
2.2.3.5 Developmental Effects
2.2.3.6 Reproductive Effects
2.2.3.7 Genotoxic Effects
2.2.3.8 Cancer
2.2.3.9 Part Per Million (PPM) Safety Ranges
5. Pilcher JD, Sollmann T. Organic, Protein and Colloidal Silver Compounds; Their Antiseptic Efficiency and Silver-Ion Content as a Basis for Their Classification. *J Lab Clin Med*, 1922;301-10.

a. The practical value of the high antiseptic efficiency of silver nitrate is limited by its side-actions: irritation and pain, astringency and corrosion. These may be largely avoided by the use of colloidal silver compounds which combine in many instances a fair degree of antiseptic action with a much smaller degree or entire absence of the irritant side-actions. The irritant and antiseptic actions of silver nitrate are due essentially to the free silver ions. The antiseptic action of the colloidal preparations has also been attributed to the presence and liberation of low concentrations of silver-ions, the concentration being so low as to be practically nonirritant, but still sufficient to be more or less antiseptic.

b. Gros concludes that the colloidal silver preparations, notwithstanding their low concentration of silver ions, may be more efficiently antiseptic, in the presence sodium chloride, than is silver nitrate, because the silver chloride from the colloidal silver forms a finer precipitate and therefore redissolves more readily than when it is precipitated from silver nitrate (except in very dilute solutions).


a. Concerning the toxicity of Ag-treated nutrients to the higher form of life, it is evident from the excellent treatise of Hill and Pillsbury that the Ag concentrations required would not be a dangerous source of argyria even when widely applied for public use. There still remains the problem of the significance of an argyrial atopy, although Hill and Pillsbury were unable to find convincing evidence that individual susceptibility enters into the development of argyria; this however does not exclude the possibility of sensitization to Ag compounds, especially when repeatedly consumed. On the other hand, silver table utensils have been used for centuries without any untoward effects; furthermore, no evidence of undesirable consequences due to consumption of Ag-treated food stuffs for extended periods of time, have been reported in Europe.

Concerning the deleterious effects Ag may have on nutrients, there is complete lack of information concerning such consequences of oligodynamic sterilization, which would be of particular interest for fruit juices preserved in this manner. It has been stated repeatedly that the preservation of the vitamin C content of fruit juices treated oligodynamically was particularly successful. Undoubtedly the Ag concentrations required for preservation, though higher than those needed for sterilization of water, are insufficient actually to cause changes in the nutrient values, with the possible exception of the different vitamins and other comparable essentials. Nothing appears to be known about Ag with vitamins, whereas an inactivation of enzymes by exposure to Ag solutions has been reported. The necessity for better information concerning these questions is evident.

In spite of the incomplete knowledge of many details involved in a more general application of the oligodynamic activity of Ag, it appears safe to state that – provided that certain difficulties in application can me mastered – Ag is an almost perfect chemical
disinfectant for substances in contact with humans and animals. In contradiction to all other agents, Ag is practically insoluble in those compounds which can occur under practical conditions.


a. 7.3.18.2 Cancer Effects. No evidence of cancer in humans has been reported despite frequent therapeutic use of silver compounds over the years. Animal studies have shown local sarcomas after the implantation of foils and discs of silver (U.S. EPA, 1998).

b. 7.3.18.3 Non-cancer Effects. The only clinical condition that is known in humans to be associated with long-term exposure to silver is argyria, a gray or blue-gray discoloring of the skin. Argyria was common around the turn of the century when many pharmacological preparations contained silver. It is much less common now. Today, case reports in humans have reported that repeated dermal contact with silver may in some cases lead to contact dermatitis and a generalized allergic reaction to silver (ATSDR, 1990b).

EPA has established an RfD for silver of 5.0E-03 mg/kg-d based on a LOAEL (adjusted) of 0.014 mg/kg-d, an uncertainty factor of 3, and a modifying factor of 1 (U.S. EPA, 1998). The RfD is based on a report summarizing 70 cases of argyria following use of silver medication in humans (Gaul and Staud, 1935, as cited in U.S. EPA, 1998).

An uncertainty factor of 3 was applied to account for minimal effects in a subpopulation that has exhibited an increased propensity for the development of argyria. The critical effect is cosmetic, with no associated adverse health effects (U.S. EPA, 1998).

EPA has medium confidence in the critical study used as the basis for the RfD because it is an old study and only describes patients who developed argyria; no information is presented on patients who received injections of silver and did not develop argyria. EPA has low confidence in the database because the studies used to support the RfD were not controlled studies, and low-to-medium confidence in the RfD because the RfD is based on a study using intravenous administration, which necessitated a dose conversion with inherent uncertainties (U.S. EPA, 1998).

Reference Concentration. EPA has not established an RfC for silver (U.S. EPA 1998).

8. The following studies suggest compelling evidence that silver is indeed safe and non-toxic:


Ref. # 86434 – Silver Sodium Hydrogen Zirconium Phosphate
Available: demonstration of not detectable (0.0004 mg/kg food) migration of Zr and Ag into food simulants under worst-case conditions of reflux; evidence of extensive leaching of silver from the additive into buffers containing sodium ions; two gene mutation assays in bacteria (negative; performed with Novaron AG300 (3.8% silver) and Novaron AG1100 (10% silver)), gene mutation assay in cultured mammalian cells (equivocal; performed with Novaron AG300); in vivo mouse micronucleus assay (negative; performed with Novaron AG300); acute toxicity data (performed with Novaron AG300 and Novaron AG1100); 13-week oral rat study (performed with Novaron AG300); teratogenicity study in rats
(performed with an experimental mixture of Novaron); dermal toxicity (performed with Novaron AG300 and AG1100); inhalation toxicity data (performed with an experimental mixture of Novaron); eye irritation data (performed with Novaron AG300); skin sensitization data (performed with Novaron AG300).

b. US EPA FQPA (Food Quality Protection Act) Implementation Activities Registered: Sildate (silver oxide) as a disinfectant and broad-spectrum preservative. EPA registration number: 3432-64.

c. American Silver L.L.C. (ASAP Solution) – colloidal silver

An LD-50 test was performed in accordance with the guidelines of the Federal Hazardous Substances Act (FHSA) Regulations, 16 CFR 1500. ASAP Solution was given to a number of both male and female test rats. The amount of ASAP Solution given to the rats was 5g/kg, or the equivalent of a 200 pound man taking 192 teaspoons of ASAP 10 ppm solution at one time.

Results: Under the conditions of the study, there was no mortality or significant evidence of toxicity observed in the rats. The test article (ASAP Solution) would not be considered toxic at a dose of 5g/kg by oral route in the rat.
Oral & I.V. Part Per Million (PPM) Safety Ranges

9. Environmental Protection Agency (EPA)/IRIS CASRN 7440-22-4 (It should be noted that the individuals tested in these case studies are members of a subpopulation of unhealthy adults.)

* Please note:
One teaspoon of 22.5 ppm Silver = 112.5 mcg.
One teaspoon of 11 ppm Silver = 55 mcg.
One teaspoon of 10 ppm Silver = 50 mcg.
10 ppm for Adult:  

a.) 7 teaspoons can be taken a day for 70 years in accordance with the reference dose

b.) 19 teaspoons can be taken a day for 70 years while remaining under the critical dose of 25 grams in a lifetime

According to the EPA Dietary Silver Intake (10 ppm)  

a. Taking 38 tspn daily of 10 ppm silver for 35 years falls below LOAEL threshold for an adult

b. Taking 76 tsp daily of 10 ppm silver for 17 years falls below LOAEL threshold for an adult

c. Taking 170 tsp daily of 10 ppm silver for 8 years falls below LOAEL threshold for an adult

d. Taking 304 tsp daily of 10 ppm silver for 4 years falls below LOAEL threshold for an adult

e. Taking 608 tsp daily of 10 ppm silver for 2 years falls below LOAEL threshold for an adult

f. Taking 200 Tbls daily of 10 ppm silver for 2 years falls below LOAEL threshold for an adult

g. Taking ¾ gallon daily of 10 ppm silver for 2 years falls below LOAEL threshold for an adult

***
11 ppm for Adult:  

a.) 6 teaspoons can be taken a day for 70 years in accordance with the reference dose  
b.) 17 teaspoons can be taken a day for 70 years while remaining under the critical dose of 25 grams in a lifetime

According to the EPA Dietary Silver Intake (11 ppm)  

a. Taking 35 tspn daily of 11 ppm silver for **35 years** falls below LOAEL threshold for an adult  
b. Taking 73 tsp daily of 11 ppm silver for **17 years** falls below LOAEL threshold for an adult  
c. Taking 155 tsp daily of 11 ppm silver for **8 years** falls below LOAEL threshold for an adult  
d. Taking 310 tsp daily of 11 ppm silver for **4 years** falls below LOAEL threshold for an adult  
e. Taking 620 tsp daily of 11 ppm silver for **2 years** falls below LOAEL threshold for an adult  
f. Taking 180 Tbls daily of 11 ppm silver for **2 years** falls below LOAEL threshold for an adult  
g. Taking ¾ gallon daily of 11 ppm silver for **2 years** falls below LOAEL threshold for an adult

***
22.5 ppm for Adult:  
  a.) 3 teaspoons can be taken a day for 70 years in accordance with the reference dose  
  b.) 8 teaspoons can be taken a day for 70 years while remaining under the critical dose of 25 grams in a lifetime

According to the EPA Dietary Silver Intake (22.5 ppm)  
  a. Taking 3 tbspn daily of 22.5 ppm silver for 60 years falls below LOAEL threshold for an adult  
  b. Taking 16 tspn daily of 22.5 ppm silver for 35 years falls below LOAEL threshold for an adult  
  c. Taking 32 tspn daily of 22.5 ppm silver for 17 years falls below LOAEL threshold for an adult  
  d. Taking 64 tspn daily of 22.5 ppm silver for 8 years falls below LOAEL threshold for an adult  
  e. Taking 128 tspn daily of 22.5 ppm silver for 4 years falls below LOAEL threshold for an adult  
  f. Taking 256 tspn daily of 22.5 ppm silver for 2 years falls below LOAEL threshold for an adult  
  g. Taking 85 tbspn daily of 22.5 ppm silver for 2 years falls below LOAEL threshold for an adult  
  h. Taking 1/3 gallon daily of 22.5 ppm silver for 2 years falls below LOAEL threshold for an adult

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5. Intravenous Administration Toxicity Data: Environmental Protection Agency Document: CASRN: 7440-22-4-0099

<table>
<thead>
<tr>
<th>Critical Effect</th>
<th>Experimental Doses*</th>
<th>UF</th>
<th>MF</th>
<th>RfD</th>
</tr>
</thead>
<tbody>
<tr>
<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 gram (total dose); converted to an oral dose of 0.014 mg/kg/day</td>
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<td>Gaul and Staud, 1935</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).
SUMMARY – Individual formulations have different inherent potentials for toxicity only as it relates to their content of non-oligodynamic silver. Oligodynamic silver is by definition non-toxic. At least one high quality and commercially available pure silver hydrosol product has been found to be over 95% oligodynamic silver by independent laboratory analysis. The key factors that improve a silver formulation’s beneficial effects appear in many instances to be the key factors that lessen toxicity. These factors are:

- Stable and finely dispersed silver solutions are thought to be more effective and less toxic than silver solutions containing larger silver particle size.
- Larger silver particle size may be more easily deposited into tissues rather than eliminated with mechanisms better suited to handle smaller particle sizes (i.e., metallothioneins, amino acids, albumin, sulphydryl and imidazole groups, WBC – bile routes of elimination, etc).
- Finer particles, having greater surface area than larger particle sizes, offer greater intervention with infectious processes.
- Stable, pure, and fine silver particles are more likely to be eliminated first through bile and then secondly through normal kidney excretion routes.

According to the 80th edition of CRC’s Handbook of Chemistry and Physics, “While silver itself is not considered to be toxic, most of its salts are poisonous… Natural silver contains two stable isotopes… Silver compounds can be absorbed in the circulatory system and reduced silver deposited in the various tissues of the body… Silver has germicidal effects and kills many lower organisms effectively without harm to higher animals.”

Medicinal solutions of silver have no known established lethal dose (LD) or LD-50 value, although one report estimates that the lethal toxic dose (LTD) ranges between 3.5 to 35 grams for an average adult. This study, however, does not specify what formulations upon which it based its conclusions (silver nitrate, silver chloride, silver arsphenamine, silver sulfadiazine, etc.). This is common to most peer-reviewed articles when presenting data on silver toxicity or argyria. It suggests that either (a) the authors are not toxicity experts with regard to silver speciation respective to the varied and diverse silver-based drugs employed over the last 100 years, or (b) there is an intention to not identify these diverse silver formulations with their significantly different toxicity characteristics.

The Agency for Toxic Substance and Disease Registry (ATSDR) does list out carefully the older varieties of different silver-based drugs, and it carefully lists the toxicities peculiar to each. However, there has been no toxicity parameters covered by ATSDR for a pure oligodynamic Ag⁺ and water solution only. And to compare such a formulation to other silver-based drugs would be akin to comparing apples to oranges. Indeed, top authorities such as regard such a formula to be the least toxic of all silver formulations, because it is simply pure silver and nothing else.

Even the most recent peer-reviewed reports on Argyria, let alone those reported in the lay press, make no distinction between toxicity differences between radically different silver formulations. For example, just the differences between the often cited older colloidal silver formulations is extraordinary: Strong Silver Protein formulations range from 7.5% to 8.5% elemental silver, while curiously Mild Silver Protein formulations range from 19% to 25% elemental silver content! In reality, the names were assigned because although the Strong Silver Protein formula contained less overall silver, its
formulation favored the liberation of more active silver ions when administered than did the Mild Silver Protein formulations. As a guideline, keep in mind that various editions of the U.S. Dispensatory consistently remarked that only 2% of the elemental silver content actually presented itself as an active form of silver ($\text{Ag}^+$) in any of these various formulations.

- And the confusion surrounding toxicity can get worse in some reports.
  
  (a) The toxicity range was extrapolated from a single murine study.
  
  (b) Extremely rare and isolated human deaths reportedly associated with silver ingestion or infusion, have been reported. However, the circumstances of such cases were so ill-defined that it is impossible to formulate any meaningful data, let alone determine any conclusions. For example, from the case histories, most of these patients appeared to be near death at the time of treatment from their condition. $^{36, 37, 38, 39}$
  
  (c) When authors cite the LTD, they do not identify over what time frame the silver was administered. Typical doses of silver given over typical time frames are not known to cause any problems. By typical, it is meant those reported in peer-review articles of their day. Presumably the LTD cited by recent reviewers was administered as an extraordinary large single dose over an atypical brief time period.$^{40}$

For emphasis we re-state that the EPA/IRIS critical oral dose figure of 14.00 mcg/kg/day only applies to a continuous daily exposure period of 70 years, resulting in a cumulative dose of twenty-five (25) grams total elemental silver. Only at this point does the only known toxic symptom occur of simple argyria, with the exceptions of (i) extremely rare and typically self-limiting allergic reactions, and (ii) readily manageable Herxheimer Effects.
References:

17. Pilcher, JD, T Sollmann, "Organic, Protein and Colloidal Silver Compounds: Their Antiseptic Efficiency and Silver-Ion Content as a Basis for Their Classification," *The Journal of Laboratory and Clinical Medicine*, 1923; p. 301-10.
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