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# Exposure-Related Health Effects of Silver and Silver Compounds: A Review

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**A critical review of studies examining exposures to the various forms of silver was conducted to determine if some silver species are more toxic than others. The impetus behind conducting this review is that several occupational exposure limits and guidelines exist for silver, but the values for each depend on the form of silver as well as the individual agency making the recommendations. For instance, the American Conference of Governmental Industrial Hygienists has established separate threshold limit values for metallic silver (0.1 mg/m$^3$) and soluble compounds of silver (0.01 mg/m$^3$). On the other hand, the permissible exposure limit (PEL) recommended by the Occupational Safety and Health Administration and the Mine Safety and Health Administration and the recommended exposure limit set by the National Institute for Occupational Safety and Health is 0.01 mg/m$^3$ for all forms of silver. The adverse effects of chronic exposure to silver are a permanent bluish-gray discoloration of the skin (argyria) or eyes (argyrosis). Most studies discuss cases of argyria and argyrosis that have resulted primarily from exposure to the soluble forms of silver. Besides argyria and argyrosis, exposure to soluble silver compounds may produce other toxic effects, including liver and kidney damage, irritation of the eyes, skin, respiratory, and intestinal tract, and changes in blood cells. Metallic silver appears to pose minimal risk to health. The current occupational exposure limits do not reflect the apparent difference in toxicities between soluble and metallic silver; thus, many researchers have recommended that separate PELs be established.**

*Keywords:* Argyria; argyrosis; occupational exposure; occupational exposure limits; silver



## INTRODUCTION

Silver is a rare but naturally occurring element. It is slightly harder than gold and is very ductile and malleable. Pure silver has the highest electrical and thermal conductivity of all metals and has the lowest contact resistance (Nordberg and Gerhardsson, 1988). Because of these properties, silver has been used in a wide variety of applications. Ancient civilizations were aware of silver's bactericidal properties (Hill and Pillsbury, 1939). Metallic silver was used for surgical prosthesis and splints, fungicides, and coinage. Soluble silver compounds, such as silver salts, have been used in treating mental illness, epilepsy, nicotine addiction, gastroenteritis, and infectious diseases, including syphilis and gonorrhea (Marshall and Schneider, 1977; Shelley *et al*., 1987; Gulbranson *et al*., 2000).

Some of the current uses of silver metal and silver compounds are listed in Table 1 (HSE, 1998; Nordberg and Gerhardsson, 1988; ATSDR, 1990; Lewis, 2001; Etris, 2001; Etris and Cappel, 2003; GFMS, 2004). During 2003, industrial applications, jewelry and silverware, and the photographic industry were the largest consumers of silver, using 40, 31 and 22%, respectively (GFMS, 2004). The photographic industry utilizes the photosensitive properties of silver halides (ATSDR, 1990). The widest and best known use of silver in medicine is in combination with sulfadiazine, where it becomes a topical antibacterial agent for the treatment of burns (Modak *et al*., 1988; Fox *et al*., 1990; Fuller *et al*., 1994; Pruitt *et al*., 1998). Colloidal silver proteins were at one time commonly used to fight colds

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Table 1. Various uses for silver metal and silver compounds

| Silver compounds | Silver and silver alloys |
|---|---|
| Photography | Jewelry |
| Batteries | Silverware |
| Bactericide | Electronic components |
| Catalysts | Heat sink |
| Medicinals | Solders |
| Lubrication | Brazing alloys |
| Cloud seeding | Superconductors |
| Window coatings | Bactericide |
| Mirrors | Dental amalgams |
| Flower preservative | Bearings |
| Electroplating | Coinage/medals |
| Sanitation of: | |
| Swimming pools | |
| Hot tubs/spas | |
| Drinking water | |
| Cosmetics | |

(Fung and Bowen, 1996) and are once again gaining popularity as a dietary supplement for treating certain diseases (Gulbranson *et al*., 2000; Silver, 2003).

Several factors influence the ability of a metal to produce toxic effects on the body; these include the solubility of the metal, the ability of the metal to bind to biological sites, and the degree to which the metal complexes formed are sequestered or metabolized and excreted (Weir, 1979). A toxic effect is defined as an undesirable or adverse health effect (James *et al*., 2000). Existing studies seem to demonstrate that some forms of silver are more toxic than others (Hill and Pillsbury, 1939; Brooks, 1981; Rosenman *et al*., 1987; Pifer *et al*., 1989; Breitstadt, 1995; Williams and Gardner, 1995). Because of the apparently different toxicities that soluble and insoluble forms of silver have on the body, the scientific literature was critically reviewed to investigate the occurrence of adverse health outcomes, with an emphasis on cases of occupational exposure.

## HEALTH EFFECTS

Silver's wide variety of uses allows exposure through various routes of entry into the body. Ingestion is the primary route of entry for silver compounds and colloidal silver proteins (Silver, 2003). Inhalation of dusts or fumes containing silver occurs primarily in occupational settings (ATSDR, 1990). Skin contact occurs in occupational settings (ATSDR, 1990), from the application of burn creams (Wan *et al*., 1991) and from contact with jewelry (Catsakis and Sulica, 1978). Silver can also gain entry into the body through the use of acupuncture needles (Sato *et al*., 1999), catheters (Saint *et al*., 2000), dental amalgams (Catsakis and Sulica, 1978), or accidental puncture wounds (Rongioletti *et al*., 1992).

Soluble silver compounds are more readily absorbed than metallic or insoluble silver (Rosenman *et al*., 1979, 1987; HSE, 1998) and thus have the potential to produce adverse effects on the human body (Weir, 1979). Acute symptoms of overexposure to silver nitrate are decreased blood pressure, diarrhea, stomach irritation and decreased respiration. Chronic symptoms from prolonged intake of low doses of silver salts are fatty degeneration of the liver and kidneys and changes in blood cells (Venugopal and Luckey, 1978). Long-term inhalation or ingestion of soluble silver compounds or colloidal silver may cause argyria and/or argyrosis (Nordberg and Gerhardsson, 1988; Fung and Bowen, 1996; Gulbranson *et al*., 2000). Soluble silver compounds are also capable of accumulating in small amounts in the brain and in muscles (Fung and Bowen, 1996). Silver in any form is not thought to be toxic to the immune, cardiovascular, nervous, or reproductive systems (ATSDR, 1990) and is not considered to be carcinogenic (Furst and Schlauder, 1978).

### *Argyria and argyrosis*

The most common health effects associated with prolonged exposure to silver are the development of a characteristic, irreversible pigmentation of the skin (argyria) and/or the eyes (argyrosis). The affected area becomes bluish-gray or ash gray and is most prominent in areas of the body exposed to sunlight (Shelley *et al*., 1987; ATSDR, 1990; Gulbranson *et al*., 2000). Argyria and argyrosis have been reported during placement of silver-containing solid materials into the skin or body (Espinal *et al*., 1996); inhalation in occupational settings (Barrie and Harding, 1947; Rosenman *et al*., 1979); and from the use of colloidal silver and silver-containing medicinals (Fung and Bowen, 1996; Gulbranson *et al*., 2000; Tomi *et al*., 2004), smoking deterrents (MacIntyre, 1978; East *et al*., 1980; Jensen *et al*., 1988; Van Garsse and Versieck, 1995), dental materials (Watanabe, 1989), and silver solder (Scroggs *et al*., 1992; Sánchez-Huerta *et al*., 2003).

Argyria and argyrosis may be classified as either localized or generalized (Greene and Su, 1987). Localized argyria is caused by direct external contact with silver. Very small silver particles may enter the body through the exocrine sweat glands or through punctures (Buckley, 1963; Buckley *et al*., 1965). These deposits, which remain in the skin indefinitely (Egli, 2000), are light brown to dark blue and look like small round or oval patches (Rongioletti *et al*., 1992). The most commonly affected areas are hands, eyes, and mucous membranes (Breitstadt, 1995). If fine particles of silver are rubbed into the eyes (i.e. in occupational settings), localized argyrosis may develop over time (Moss *et al*., 1979;

Breitstadt, 1995). Localized argyria can also occur following the application of silver compounds to wounds (Buckley, 1963; Fisher *et al*., 2003).

Generalized argyria is recognized by a widespread pigmentation of the skin, eyes, and nails. Generalized argyria and argyrosis may result when silver compounds are applied to mucosal surfaces, inhaled, ingested, or injected into the body (Hunter, 1969; Rosenblatt and Cymet, 1987). After silver enters the body, it is absorbed, carried by the bloodstream and deposited in various tissues throughout the body. Areas of the body most likely to become pigmented include eyes, internal organs, and sun-exposed areas such as the face, ears, forearms, hands, and nails (Juberg and Hearne, 2001). Generalized argyria was most often reported following the ingestion or application of silver-containing medicines, but it has also been reported after occupational exposure among silver nitrate makers (Smith and Carson, 1977; Rosenman *et al*., 1979; Jongerius and Jongeneelen, 1992).

### *Respiratory effects*

Inhalation of soluble silver compounds has been reported to cause both upper (nose and throat) and lower (chest) respiratory tract irritation (Rosenman *et al*., 1979), although irritation is most likely caused by the corrosive effect of nitrate in some silver compounds rather than by silver itself (Rosenman *et al*., 1979, 1987; Pifer *et al*., 1989).

Staining of alveoli and bronchial tissue may occur after inhaling silver dust or fumes, but this apparently is not harmful to health (Brooks, 1981). However, bronchitis, emphysema and a reduction in pulmonary volume were observed when silver polishers were exposed to metallic silver, as well as to other metals (Barrie and Harding, 1947; Perrone *et al*., 1977; Rosenman *et al*., 1979).

### *Tissues and organs*

Normal concentrations of silver in human tissues are low. If there is overexposure, silver can accumulate in the skin, liver, kidneys, corneas, gingiva, mucous membranes, nails and spleen (Rosenman *et al*., 1979; Wan *et al*., 1991; Hollinger, 1996; Sue *et al*., 2001). Silver ions possess a high affinity for the thiol groups in the liver (Baldi *et al*., 1988) and have been shown to bind to reduced glutathione and be transported into the bile, thus depleting the amount of reduced glutathione available for biochemical pathways. Reduced glutathione plays an important role in maintaining proper structure and function of red blood cells, as well as eliminating organic peroxides (Baldi *et al*., 1988). Even though silver does accumulate in some organs and tissues, very little data are available that indicate possible toxic effects. Venugopal and Luckey (1978) noted that argyria can be considered a mechanism to detoxify silver by sequestering it in the tissues as harmless silver-protein complexes or silver sulfide.

### *Metabolism*

Ingested silver compounds are estimated to be absorbed by the body at a level of at most 10%, with only ∼2–4% being retained in tissues (Furchner *et al*., 1968; Klein, 1978). Silver can be measured in urine, blood, and feces. Even though the body eliminates silver primarily in feces (Newton and Holmes, 1966; Furchner *et al*., 1968; Phalen and Morrow, 1973), it can be accurately determined in whole blood (Armitage *et al*., 1996) and is, therefore, the biological medium of choice due to collection convenience. Urinalysis is useful only following a high degree of exposure because little silver is excreted in urine (Phalen and Morrow, 1973; Juberg and Hearne, 2001).

Many researchers attribute the pigmentation process associated with generalized argyria solely to soluble silver compounds (Hill and Pillsbury, 1939; Brooks, 1981; Rosenman *et al*., 1987; Wobling *et al*., 1988; Pifer *et al*., 1989; ACGIH, 1991; Breitstadt, 1995; Williams and Gardner, 1995) because metallic silver and insoluble silver compounds are not readily taken up by the body (Grabowski and Haney, 1972; Breitstadt, 1995). It is thought that when the body absorbs silver compounds, they form complexes primarily with proteins, but also with RNA and DNA, by binding to sulfhydryl, amino, carboxyl, phosphate and imidazole groups (Danscher, 1981; ATSDR, 1990; Fung and Bowen, 1996).

Light acts as a catalyst by triggering the photo-reduction of these compounds to form metallic silver, similar to the process involved when developing a negative in photography (Shelley *et al*., 1987; Gulbranson *et al*., 2000). Metallic silver is subsequently oxidized by tissue and is bound as silver sulfide (Danscher, 1981). Black silver sulfide and silver selenide complexes bound to tissue were identified as comprising the silver particles deposited in many individuals with argyria (Aaseth *et al*., 1981; Berry and Galle, 1982; Rongioletti *et al*., 1992). These compounds may then stimulate increased melanin production, particularly in sun-exposed areas, which leads to pigmentation (Buckley *et al*., 1965; Greene and Su, 1987; Fung and Bowen, 1996; Williams, 1999). The pigmentation resulting from silver deposition is irreversible. Chelation therapy and dermabrasion are ineffective in removing silver deposits from the body (Aaseth *et al*., 1981; Fung and Bowen, 1996; Egli, 2000). There is no effective treatment for argyria (Green and Sue, 1987).

## EXPOSURE LIMITS

The Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA) currently enforce a Permissible

Exposure Limit (PEL) of 0.01 mg/m$^3$ for metallic and soluble silver compounds (OSHA, 1989; NIOSH, 2003). The National Institute for Occupational Safety and Health (NIOSH) established a Recommended Exposure Limit (REL) of 0.01 mg/m$^3$ for both soluble silver compounds and silver metal dust, which does not differ from the OSHA PEL (NIOSH, 1992).

In 1966, the American Conference of Governmental Industrial Hygienists (ACGIH) established a Threshold Limit Value (TLV) of 0.01 mg/m$^3$ for all forms of silver (ACGIH, 2001), largely based on Hill and Pillsbury's (1939) publication. However, in response to findings from studies undertaken since Hill and Pillsbury's work, in 1980 ACGIH set a new TLV of 0.1 mg/m$^3$ for metallic silver. ACGIH recognized the different outcomes from exposure to soluble and/or insoluble silver, rationalizing that 'the available data on soluble compounds of silver demonstrate that silver salts have a greater propensity to cause argyria than does the dust or fume of metallic silver and that the respective exposure levels of 0.01 mg/m$^3$, for soluble silver, and 0.1 mg/m$^3$, for metallic silver, are adequate to prevent argyria in workers exposed to airborne silver' (ACGIH, 1991).

ACGIH is not the only organization to note different health outcomes from exposure to the different forms of silver. In 1994, the European Commission, assisted by a scientific expert group on occupational exposure limits, recommended an 8 h time-weighted average (TWA) of 0.1 mg/m$^3$ total silver dust (European Commission, 1994). The Health and Safety Executive of the United Kingdom also reached a similar conclusion after investigating metallic silver, stating 'from the data available it is concluded that exposure to ~0.1 mg/m$^3$ 8 h TWA of metallic silver would not result in a significant development of pigmentations' (HSE, 1998). Australia, Belgium, Finland, France, and Sweden have also separated exposure levels to metallic silver and soluble silver at 0.1 and 0.01 mg/m$^3$, respectively (NIOSH, 2003).

Argentina, Bulgaria, Columbia, Jordan, Korea, New Zealand, Singapore and Vietnam recognize the ACGIH TLV of 0.1 mg/m$^3$ for silver metal, while Austria, Denmark, Germany, Japan, The Netherlands, Norway, and Switzerland recognize 0.01 mg/m$^3$ as the occupational exposure limit for all forms (NIOSH, 2003).

## SELECTED CASE STUDIES

Table 2 summarizes the health effects associated with exposure to various forms of silver. Most studies discuss the effects of silver on the human body following intentional ingestion of silver compounds. A number of studies also describe the effects of occupational exposure to metallic, insoluble and soluble silver compounds.

### *Medicinal, therapeutic and unintentional exposure*

As discussed earlier, silver is very effective at eliminating bacterial infections (Hill and Pillsbury, 1939; Silver, 2003) and so has been extensively used in the past for medicinal purposes. The medical literature cites numerous cases of argyria appearing after the use of silver-containing preparations. Hill and Pillsbury (1939) analyzed data from 357 recorded cases of argyria and argyrosis. Of the 357 cases, 317 followed therapeutic use of colloidal silver and silver compounds and the remaining 40 were due to occupational exposure to various silver compounds and metallic silver.

Colloidal silver protein has been used as an allergy and cold medication (Jacobs, 1998; Bouts, 1999; Gulbranson *et al*., 2000; Tomi *et al*., 2004), in eye drops to alleviate soreness (Loeffler and Lee, 1987) and for the treatment of various ailments (White *et al*., 2003). The adverse affects from extended use of colloidal silver protein in these cases were grossly discolored fingernails, ocular argyrosis, and generalized argyria. The location and degree of discoloration depends on the mode of application (i.e. nose spray or eye drops) as well as individual susceptibility (Fowler and Nordberg, 1986).

A number of cases of generalized argyria were reported following the use of anti-smoking tablets (Van Garsse and Versieck, 1995), lozenges (MacIntyre, 1978; Shelton and Goulding, 1979), and gum (Jensen *et al*., 1988) that contained silver acetate, as well as following the habitual use of silver foil-coated mouth refresheners (Sato *et al*., 1999).

Generalized argyria occurred after using a topical solution of silver nitrate three times a week for 2.5 years to control gingival bleeding. Severe pigmentation developed and the patient no longer appeared to be Caucasian. During an abdominal operation (unrelated to the argyria), silver deposits were reported in her liver, spleen, intestines, and pancreas (Marshall and Schneider, 1977). Others have also reported generalized argyria after the use of silver nitrate to treat an intestinal ulcer (Steininger *et al*., 1990) and oral ulcerations (Aaseth *et al*., 1981; Lee and Lee, 1994).

A few cases of localized or generalized argyria have been reported following the use of silver sulfadiazine cream for the treatment of wounds. One patient developed localized argyria in a scar after silver sulfadiazine cream was applied to a post-surgical wound (Fisher *et al*., 2003). In another case study, a 1% silver sulfadiazine cream was applied to leg ulcers for 5 months. The patient developed generalized argyria and the area around the ulcers became severely discolored (Payne *et al*., 1992).

Mild allergenic responses have been attributed to dermal contact with some silver compounds (Marks, 1966; Catsakis and Sulica, 1978; ATSDR, 1990).

Table 2. Health effects associated with various forms of silver

| Source of silver | Outcome and/or health effects | References |
|---|---|---|
| Medicinal | | |
| Silver nitrate—oral ulcerations | Argyria | Aaseth *et al*., 1981; Lee and Lee, 1994 |
| Silver nitrate—topical for gingival bleeding | Argyria, silver deposits in organs[a], and abdominal pain | Marshall and Schneider, 1977 |
| Silver nitrate solution—varicose veins | Argyria | Shelley *et al*., 1987 |
| Silver acetate—antismoking gum, lozenges, and tablets | Argyria | Jensen *et al*., 1988; MacIntyre, 1978; Van Garsse and Versieck, 1995 |
| Colloidal silver protein—allergy and cold med. | Argyria and high blood-silver levels | Gulbranson *et al*., 2000 |
| Colloidal silver protein—treatment of ailments | Argyria | White *et al*., 2003 |
| Silver protein—nose drops | Argyria | Jacobs, 1998 |
| Colloidal protein—eye drops | Argyrosis | Loeffler and Lee, 1987 |
| Colloidal silver and silver compounds | Argyria, argyrosis | Hill and Pillsbury, 1939 |
| Silver coated pills—mouth freshener | Argyria | Sato *et al*., 1999 (case 1) |
| Silver coated acupuncture needles | Argyria | Sato *et al*., 1999 (case 2) |
| Silver in water—hemodialysis therapy | Argyria | Sue *et al*., 2001 |
| Occupational | | |
| Soluble | Elevated blood-silver levels | Armitage *et al*., 1996 |
| Soluble | Argyrosis, elevated blood-silver levels | Williams, 1999 |
| Soluble | Argyria, argyrosis, abdominal pain | Rosenman *et al*., 1979 |
| Soluble | Argyrosis, abdominal pain[b], nosebleed[b], respiratory irritation, allergic response | Rosenman *et al*., 1987 |
| Soluble | Argyria, ocular argyrosis | Moss *et al*., 1979 |
| Soluble | Argyria, argyrosis | Wobling *et al*., 1988 (soluble group) |
| Soluble | Argyrosis | Williams and Gardner, 1995 (case 2) |
| Soluble | Argyria | Buckley, 1963 |
| Metallic | Argyro-siderosis of the lungs | Barrie and Harding, 1947 |
| Metallic | No health effects | Linnett and Bradford, 1996 |
| Insoluble | Severe circulatory and respiratory symptoms[c] | Forycki *et al*., 1983 |
| Insoluble | Argyrosis | Pifer *et al*., 1989 |
| Insoluble | No health effects | DiVincenzo *et al*., 1985 |
| Insoluble | No health effects | Breitstadt, 1995 |
| Insoluble | No health effects | Williams and Gardner, 1995 (case 1) |
| Insoluble | No health effects | Wobling *et al*., 1988 (insoluble group) |

[a]Organs involved were liver, spleen, intestines and pancreas.
[b]Effects thought to be caused by cadmium, not silver.
[c]Injuries appeared to be due to inadequate ventilation, not the toxic effects of metallic silver vapors.

A worker developed a rash on his forearms, face, and neck after exposure to a silver cyanide solution (Heyl, 1979).

Three cases of localized argyria were caused by silver earrings (Van den Nieuwenhuijsen *et al*., 1988; Shall *et al*., 1990; Sugden *et al*., 2001). All three cases were due to the cutaneous implantation of a silver earring backing, either in the ear lobes or directly behind the ear. Discoloration was confined to the skin around the embedded earring backings. Two cases of localized argyria occurred after years of acupuncture therapy. In both cases, silver acupuncture needles had been implanted in the skin for >10 years and blue–black spots developed in various areas on their bodies (Tanita *et al*., 1985; Sato *et al*., 1999).

### *Occupational exposure to soluble silver compounds*

Thirty workers from an industrial plant involved with manufacturing silver nitrate and silver oxide were examined for argyria and ocular argyrosis (Rosenman *et al*., 1979). This cross-sectional study revealed that six individuals had generalized argyria and 20 had argyrosis. Personal air sampling conducted 4 months prior to the study determined a range of silver concentrations from 0.039 to 0.378 mg/m$^3$

for an 8 h TWA, suggesting that better engineering controls were needed to minimize workers' exposure to silver. Ten of the 30 workers complained of abdominal pain. This symptom was significantly associated with silver in the blood. Decreased vision at night, of which 10 workers complained, was associated with duration of employment; however, no changes in visual function could be attributed to silver deposits. Although some of these workers were diagnosed with argyria and argyrosis, the authors concluded that the health of these workers was not adversely affected. However, the permanent discoloration and the potential effect on night vision suggest the need to limit exposure to silver.

Moss *et al*. (1979) studied the same group of workers as Rosenman *et al*. (1979) and also found evidence of argyrosis in these workers. Moss *et al*. surveyed the workers and found that 27 of 30 workers had suffered burns of the skin from contact with silver nitrate and 11 workers had a history of ocular burns. An in-depth ophthalmic examination was conducted to determine if the workers suffered from any visual deficits from their exposures. Part of this examination included the use of a slit lamp. A slit lamp is a microscope with a light attached that allows the doctor to look at the conjunctiva, cornea, lens and iris. The most frequently noted abnormal finding was discoloration of the conjunctiva and/or cornea. A direct relationship was shown between the amount of discoloration of the cornea and the length of time worked. Even though 10 workers complained of decreased night vision, which correlated significantly with corneal and conjunctival silver deposition and with duration of occupational exposure, no functional deficits were found.

A later study by Rosenman *et al*. (1987) was conducted at a company that manufactured silver and other metal powders. Silver nitrate, silver oxide, silver chloride, and silver cadmium were among the powders produced. At the time of the study, OSHA measured airborne silver concentrations in the range of 0.04–0.35 mg/m$^3$. All employees who had worked for a minimum of 2 years in the silver flake, silver nitrate, or silver powder operations, as well as in the refinery, were invited to participate in the study. Ninety-six percent of the workers had elevated urine silver concentrations, and 92% had elevated blood silver concentrations. Out of 27 workers, 15 complained of upper respiratory irritation, such as itchy, red, or watery eyes; sneezing; stuffy or runny nose; and sore throat. Eight workers complained of nosebleeds, and 6 complained of decreased night vision. Slit lamp examinations revealed that 17 workers had conjunctival deposits and 6 had corneal deposits. Even though workers with corneal silver deposits were 3.5 times more likely to report problems with night vision, the association was not statistically significant. The extent of respiratory irritation caused by these compounds was inconclusive because silver oxide and nitrate, by nature, are irritants. Kidney function was also evaluated. Creatinine clearance was significantly depressed and urinary *N*-acetyl-β-D glucosaminidase (NAG) was significantly higher in the exposed group compared with unexposed controls. Kidney function appears to be adversely affected but because of concurrent exposure to known nephrotoxins, such as cadmium and solvents, the authors could not definitively determine if silver was responsible.

Blood silver concentrations in 98 occupationally exposed workers and 15 controls were assessed (Armitage *et al*., 1996). The six factories that participated in the study were involved in bullion production, silver chemical manufacturing, jewelry manufacturing, silver reclamation, and production of tableware. The majority of the workers were exposed to both metallic and soluble silver ($n = 89$). Workers classified as melters, refiners, and silver nitrate producers were found to have the highest blood-silver levels, with values ranging from 0.1 to 20 μg/l. The mean silver blood level for the control group was <0.1μg/l. No evidence of argyria was found in any of these workers.

Williams (1999) conducted a case study of a 51-year-old man who spent 7 years as a silver refiner. This individual was exposed specifically to silver nitrate and silver oxide. Personal breathing samples showed air silver concentrations of 0.11–0.17 mg/m$^3$. An ophthalmologist diagnosed this individual with corneal and conjunctival argyrosis, but normal vision. This individual was followed for an additional 5 years as he continued working in the silver refinery. Clinical examinations reported no evidence of generalized argyria, nor was there progression of the argyrosis.

Buckley (1963) reported a case study of a woman whose fingers were repeatedly exposed to a photographic silver-fixing solution for several months. Discoloration was confined to where her fingers had come into direct contact with the silver solution. Specimens of the skin were removed from the fingers using an electric punch and examined with an electron microprobe X-ray analyzer. Buckley concluded that silver salts entered her skin through the sweat glands and were deposited just under the skin surface. To prevent this type of localized argyria, proper personal protective equipment should be worn.

### *Occupational exposure to metallic silver and insoluble silver compounds*

A group of industrial silver plant workers was studied to determine if symptoms of exposure differed between those predominantly exposed to insoluble silver ($n = 26$) and those exposed exclusively to soluble silver compounds ($n = 23$) (Wobling *et al*., 1988). Ten subjects not occupationally exposed to silver were used as a control group. Length of exposure ranged from 3 to 20 years, and exposure levels ranged from 0.001 to 0.310 mg/m$^3$ for the soluble group and from 0.003 to 0.540 mg/m$^3$ for the insoluble group. In the soluble group, discoloration was observed in the eyes (argyrosis) of 5 workers, the mouth of 2 workers, the nose of 1 worker and the nape of the neck of 1 worker. No symptoms of argyria or argyrosis were seen in the insoluble group. Skin biopsies analyzed for silver revealed a range of 0.03–13.48 p.p.m. for the soluble group (median 0.115 p.p.m.), 0.03–0.77 p.p.m. for the insoluble group (median 0.085 p.p.m.) and 0.01–0.11 p.p.m. for the control group (median 0.02 p.p.m.). Silver concentrations found in skin biopsies and air did not correlate with either ocular deposits or duration of exposure. The authors concluded that the occurrence of argyria and argyrosis is dependent upon individual susceptibility.

The absorption and excretion of silver was monitored by measuring blood, urine, fecal, and hair concentrations from 37 workers occupationally exposed primarily to insoluble silver compounds; a group of 35 occupationally unexposed workers served as a control population (DiVincenzo *et al*., 1985). Airborne silver concentrations ranged from 0.001 to 0.1 mg/m$^3$ in the occupationally exposed group. Measured concentrations of silver in blood, urine, feces and hair were 0.011 μg/ml, <0.005 μg/g, 15 μg/g and 130 ± 160 μg/g, respectively, for the exposed workers and <0.005 μg/ml, <0.005 μg/g, 1.5 μg/g and 0.57 ± 0.56 μg/g, respectively, for the control group. Using fecal excretion as an index of exposure for calculating body burden of silver and assuming that 1–5% of the silver was retained in the body (Scott and Hamilton, 1950; Furchner *et al*., 1968), a minimum of 24 years of continuous workplace exposure would be necessary for workers to retain enough silver to develop argyria. The researchers concluded that generalized argyria was not likely to occur in workers exposed to insoluble forms of silver at concentrations in the range specified above.

Twenty-seven silver reclamation workers exposed primarily to insoluble silver halides were clinically evaluated for silver exposure (Pifer *et al*., 1989). An equal number of occupationally unexposed workers were selected as a control group. Airborne silver concentrations ranged from 0.005 to 0.240 mg/m$^3$. Mean concentration of silver in the blood of 21 silver reclamation workers was 0.01 μg/ml. Only one worker had a detectable level of urinary silver; silver was not detected in the blood or the urine of the control group. Silver was measured in all fecal samples collected, and mean concentrations were 16.8 and 1.5 μg/g for 18 exposed workers and 22 controls, respectively. Clinical examinations and skin biopsies revealed no cases of generalized argyria. Twenty of the 27 silver workers exhibited some degree of internal nasal septal pigmentation. Seven out of 24 workers were found to have ocular silver deposits in the conjunctiva and/or cornea. Optometric and contrast sensitivity test results revealed no significant deficits in visual performance. No abnormalities were revealed during tests of renal function, pulmonary function, and chest radiographs. The researchers concluded there was no evidence supporting the notion that chronic exposure to insoluble silver halides had any detrimental health effects on exposed workers at the concentration levels measured. They also concluded that silver speciation should be considered when assessing the effects of silver on human health.

An unpublished report obtained from Johnson Matthey (Linnett and Bradford, 1996) discusses a study of 41 workers from the United Kingdom, who were involved in the recovery and recycling of silver. None of the workers showed signs of argyria or argyrosis even though past exposure to metallic silver exceeded 0.1 mg/m$^3$. Their length of employment ranged from 3 months to 29 years. Median exposure in 1976–1977 was 0.25 mg/m$^3$, and the geometric mean from 1987 to 1996 was 0.52 mg/m$^3$. The researchers concluded that metallic and soluble forms of silver should be distinguished when setting exposure limits and that 0.1 mg/m$^3$ is a safe exposure level for metallic silver.

A small number of workers ($n = 9$) in the study by Armitage *et al*. (1996) were exposed primarily to metallic silver. This group of workers was involved in producing small intricate items of jewelry. The blood-silver concentrations were much lower (0.2–2.8 μg/l) than in those workers exposed to soluble compounds of silver. Again, no evidence of argyria was found in these workers.

Forycki *et al*. (1983) discussed the case of a man who was exposed to a very high concentration of metallic silver vapors. The man was working in a very small, uncontrolled, enclosed work area while melting silver ingots. He was hospitalized ~36 h after exposure because of severe circulatory and respiratory symptoms. He had to breathe with the help of an artificial respirator for 18 days. He later recovered completely and went back to work. The injuries in this case appear to have been caused by improper ventilation and exposure to an extremely high concentration of metal fumes in an uncontrolled work environment, rather than because of the toxic effects of metallic silver vapor.

Perrone *et al*. (1977) conducted a study of four workers involved in polishing silver cutlery. The polishing process involved the use of abrasive pastes and a cloth or vegetable fiber buffing wheel. The length of exposure ranged from 19 to 31 years. All four workers had deposits on the conjunctiva and/or the cornea. No generalized argyria was observed. Respiratory function tests revealed a reduced lung capacity and carbon monoxide transfer. Since all four workers were smokers and the work environment included multiple agents, the role of silver exposure could not definitively be assessed.

A study of two men occupationally exposed to silver was conducted by Williams and Gardner (1995). The first was a process operator with 3 years experience exposed primarily to insoluble silver compounds, and the second was a process operator with 7 years experience exposed primarily to soluble silver compounds. In the case of the first worker, no evidence was seen of argyria or argyrosis or silver deposition in the nasal or oral mucosa. Atmospheric concentrations of silver were 0.085 $mg/m^3$ recorded at the incinerator and 1.03–1.36 $mg/m^3$ recorded in the pulverizing area, suggesting that the potential for exposure was significantly above the occupational exposure limit. Blood-silver concentration was 49 μg/l. The second worker was employed in a silver refinery. No evidence of argyria was seen, but argyrosis was evident as a gray pigmentation of the conjunctiva. Atmospheric silver concentrations were recorded at levels of 0.03 to 0.17 $mg/m^3$ in locations where the worker was exposed. Blood-silver concentration was 74 μg/l.

When the majority of exposure is to the insoluble compounds of silver, as is the case with the first worker, the results of this study agree with the observations of others (DiVincenzo *et al*., 1985; Wobling *et al*., 1988; Pifer *et al*., 1989) on the relatively benign nature of insoluble silver compounds. The case of the second worker, who developed argyrosis, also agrees with the findings of others regarding mixed exposures or exposures primarily to soluble forms of silver (Moss *et al*., 1979; Rosenman *et al*., 1979; Wobling *et al*., 1988).

## DISCUSSION

Over the last several decades, the use of silver-containing medicinals prescribed by physicians decreased dramatically as the use of antibiotics increased. However, colloidal silver and silver salts are once again being promoted as a cure-all for various diseases. The Food and Drug Administration (FDA) 'is not aware of any substantial scientific evidence that supports the use of over-the-counter colloidal silver ingredients or silver salts for disease conditions,' and has declared that 'all over-the-counter drug products containing colloidal silver ingredients or silver salts are not generally recognized as safe and effective' (Federal Register, 1999). The majority of the authors of case studies involving medicinal exposure described in this paper cautioned against the long-term use of silver-containing preparations and also stressed the importance of eliminating their uncontrolled use. With a lack of regulations on food supplements, consumers are allowed to purchase products that are not approved by the FDA and that are potentially toxic. Since colloidal silver can be freely purchased as a supplement in health food stores and over the Internet, cases of argyria and argyrosis, like the ones described by Gulbranson *et al*. (2000), White *et al*. (2003) and Tomi *et al*. (2004), will most likely continue.

The body's uptake of silver is often much higher when taken orally as medication, as opposed to occupational exposure, which is predominantly through inhalation. The majority of occupational exposure reports involve soluble silver compounds, which seem to cause toxic effects at lower concentrations than metallic silver and insoluble silver compounds. For example, silver concentrations in skin biopsies found by Wolbling *et al*. (1988) and blood-silver concentrations found by Williams and Gardner (1995) and Armitage *et al*. (1996) were considerably higher in workers exposed to soluble silver compounds than in workers exposed to metallic silver or insoluble silver compounds.

Metabolism studies indicate that soluble silver compounds are absorbed by the body more readily as a result of their ability to bind to proteins, DNA and RNA. Soluble silver compounds can be quickly taken up in the bloodstream (Jongerius and Jongeneelen, 1992), deposited throughout the body, and subsequently reduced by light to metallic silver. Finally, accumulated silver can be oxidized to silver sulfide or silver selenide, resulting in blue-gray pigmentation. Metallic silver is not soluble in aqueous solutions nor is it readily solubilized by any physiological mechanisms (Grabowski and Haney, 1972; Weir, 1979); therefore, it is poorly absorbed after exposure and is more likely to be excreted by the body than is soluble silver (HSE, 1998).

In many of the studies, silver could not be definitively linked to an adverse health outcome due to the presence of confounders. The study by Rosenman *et al*. (1987) attempted to assess the effects of silver on kidney function. Creatinine clearance was significantly depressed and urinary NAG was significantly higher in the exposed group. However, it was difficult to determine if silver caused any adverse effect on kidney function because the workers had also been exposed to other agents that were known nephrotoxins.

Several cross-sectional studies were conducted where argyrosis was the most frequently reported abnormal finding. Many of the workers in these studies complained of decreased vision at night, but none showed a functional deficit in their vision. In most studies where ophthalmic examinations were conducted, decreased vision at night was associated with duration of exposure and corneal silver deposition; however, the associations were seldom statistically significant. The lack of statistical significance is most likely due to the small sample size of these studies. Additional studies could be undertaken that would employ a large enough sample size to determine if certain outcomes are statistically significant. Also, future studies should minimize the presence of confounders, which was a major limitation for most of the occupational studies reviewed.

## CONCLUSIONS

Many arguments can be made for the need to differentiate occupational exposure limits based on the different forms of silver. Some studies indicated insoluble silver levels have been tolerated without any health effects at levels 10–100 times higher than OSHA's current PEL of 0.01 mg/m$^3$, as well as ACGIH's TLV of 0.1 mg/m$^3$ (Wobling *et al*., 1988; Breitstadt, 1995; Williams and Gardner, 1995; Linnett and Bradford, 1996). Many of these researchers have recommended that occupational exposure levels to insoluble and metallic silver be reconsidered and that the standards for metallic and insoluble silver be established without any consideration of the toxicity of soluble silver compounds (Weir, 1979; Pifer *et al*., 1989; European Commission, 1994; Breitstadt, 1995; HSE, 1998; ACGIH, 2001).

Due to improved work conditions, more emphasis on safety and health in the workplace, and better engineering controls, future cases of occupational argyria or argyrosis will be extremely rare. Although the number of occupational epidemiological studies evaluating workers' exposure to all forms of silver is limited, the fact that silver has been in use for thousands of years and the most notable adverse health effect is argyria and/or argyrosis, additional studies would most likely come to the same conclusions, i.e. metallic silver has minimal effect on the human body and soluble silver compounds are more likely to produce argyria and argyrosis; therefore, separate PELs should be established.

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