

Silver

Miraculous Cure-All or Toxic Heavy Metal?

A Historical Review of Silver's Harmful Effects on Humans

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Introduction

Silver is a relatively rare metal in the earth's crust, often found deposited as a metal ore in association with other metals such as lead, copper, nickel, and zinc. It is a member of the second transition series on the periodic table (Ag, or *argentum*) and is one of the noble and heavy metals. Along with gold, it is considered a precious metal. It is slightly harder than gold, very ductile and malleable, and has the highest electrical and thermal conductivity and lowest contact resistance of all the metals (Petering 1976; Drake and Hazelwood 2005). Because of these attractive properties, it has been used for millennia in a myriad of applications, including jewelry, utensils, coins, photography, electronics, and many industrial processes. It is also a very effective antimicrobial, and is used widely in medical and health applications.

In recent years, the use of silver is skyrocketing, especially with the advent of nanotechnology, which has allowed the intentional creation of silver particles in the nanometer size range—often referred to as “nanosilver”—that can have novel properties and can be readily incorporated into a variety of materials including numerous consumer products (Wijnhoven, Peijnenburg et al. 2009). As consumer, medical, electronic, and industrial products containing colloidal silver, nanosilver, and other kinds of silver compounds become more prevalent in recent years, human and environmental exposures to silver in a variety of forms will rise, and some scientists are calling for increased attention to the potential environmental and health effects of these exposures (Hollinger 1996; Silver 2003; Silver, Phung et al. 2006; Lansdown 2007; Luoma 2008).

Current discussions among U.S. regulatory agencies about the safety of nano-sized forms of silver, in particular, are focused on the question of whether recently engineered nano-sized forms pose new health risks as compared to forms of silver that have been on the market for well over 100 years.¹ Unlike other heavy metals—such as mercury, cadmium, lead—silver is widely assumed to be relatively non-toxic to humans beyond cosmetic effects, particularly a blue-gray coloring of the skin called argyria. The assumption has shaped risk assessments and regulations on silver in the United States for a long time, and has encouraged—or at least not discouraged—the increasingly ubiquitous use of various forms of silver in recent years and silver's widespread promotion as a cure-all for a plethora of diseases and conditions.

¹ See recent documents on regulatory dockets regarding silver/nanosilver: e.g.: <http://www.regulations.gov/search/Regs/home.html#docketDetail?R=EPA-HQ-OPP-2009-1012>

Yet experimental studies on silver suggest that it can in some circumstances cause significant toxic effects in mammalian cells and organisms, and there are relatively few studies on its human health effects other than short-term clinical studies related to argyria or silver poisoning cases (often post-mortem). A number of these studies suggest that silver may not be completely innocuous to humans, and several scientists have noted that perhaps silver's toxicity to humans should be re-evaluated as its uses increase dramatically (Hollinger 1996; Lansdown 2007)

In this paper, I briefly outline experimental studies showing that various forms of silver can have toxic effects and then describe a wide range of case reports and research studies on silver going back decades that have suggested that it may also cause negative effects in exposed humans. I do not critically review technical details of these studies or compare them with studies that found evidence that silver is safe or non-toxic—but rather, I highlight red flags in these studies (usually raised by the authors themselves) and outline key unknowns and data gaps. In conclusion, I discuss questions raised by the development of engineered forms of nanosilver in recent decades and the inevitable rise in human exposures as it is used ubiquitously through society.

Silver's "Magical" History and Current Uses

Silver has a long and colorful history. It was mentioned in *Genesis* 23:16, and has been mined, manufactured, and used by humans in many cultures for a myriad of applications for thousands of years (Hill and Pillsbury 1939; Petering 1976; Silver, Phung et al. 2006). It was purportedly known to the Chaldeans as early as the fourth millennium B.C., and silver items have been found in ancient tombs of Chaldea, Mesopotamia, Egypt, China, Persia, and Greece. Silver played extremely important roles in the development of the New World because silver deposits are largely found in the Americas (especially Mexico).²

Silver's earliest uses as a medicinal originated in ideas from a combination of alchemy, chemistry, medicine, astrology, and mythology. Silver nitrate was mentioned in 69 B.C. in a pharmacopeia published in Rome, and in the writings of the Geber (700s A.D.) of the "Mohammedan school," whose teachings were based on a combination of astrology and alchemy (Hill and Pillsbury 1939). During the 14th and 15th centuries, many people followed the "ancient Chaldaic Pantheism," which taught the doctrine of "anima mundi." Anima mundi applied to "substances which could be extracted by fire," such as the seven metals known at the time—gold, silver, quicksilver (mercury), iron, copper, tin, and lead—thought by alchemists to "connect the

² More information about the history of silver mining can be found here: http://www.silverinstitute.org/silver_history.php

things of Heaven and earth” and “each metal corresponded to a part of the human body as well as to the planets” (Hill & Pillsbury? p. 2). Silver was thought to be connected to the Moon and to the brain; because the moon was thought to be related to brain disorders, silver was used for epilepsy and insanity and was referred to as “Luna” by alchemists (the origin of the common name “lunar caustic” for silver nitrate).³

Silver’s antimicrobial properties, known for thousands of years, are the most common reasons for its use in medicine historically and to this day (Silver, Phung et al. 2006). Silver was used widely during the Middle Ages as an antimicrobial and for other health problems. Theophrastus Bombastus Paracelsus (Paracelsus), an influential physician and chemist who lived from 1493-1541, commonly prescribed silver nitrate for internal uses (Petering 1976; Klasen 2000). Silver was used throughout the 1700s and 1800s for ulcers, lesions, warts, venereal diseases, bone inflammations, burn treatment, and more. In the 1800s, a “silver nitrate stick” or “porte-pierre” was a standard piece of equipment for every surgeon, used primarily for cauterizing and sterilizing wounds (Klasen 2000). Silver nitrate sticks are still used by some doctors today. In 1884 K.S.F. Crede, a German obstetrician, introduced the practice of putting silver nitrate solution in newborn children’s eyes to prevent gonorrhea, and silver compounds are still used in newborn infants eyes in some states in the U.S. (Silver, Phung et al. 2006). In the early 1900s silver arsphenamine was used to treat syphilis,⁴ and other forms of silver were used throughout this century as abortifacents and urethral sterilants (Humphreys and Routledge 1998; Lansdown 2007).

Currently, a variety of silver compounds are used ubiquitously in medicine and healthcare to prevent infections in burns, traumatic wounds, and diabetic ulcers, as well as coating of medical catheters and other medical devices implanted into the body. It is widely used as an antimicrobial in water filters and in water treatment systems. It is also becoming popular to use silver, particularly nano-sized⁵ forms (called “nanosilver”), for coating surfaces in food and agricultural processing facilities to prevent outbreaks of food-borne pathogens and in a huge variety of consumer products. In particular, the uses of silver compounds as antimicrobials in homes and public facilities are

³ Some of these beliefs are still evident today on websites promoting silver as a health remedy.

⁴ In the Tuskegee syphilis experiment, a form of silver arsphenamine (commercial name Salvarsan) was given to African American patients as one of the alternatives to penicillin (though it was found to be toxic and only mildly effective): http://en.wikipedia.org/wiki/Tuskegee_syphilis_experiment

⁵ The term “nano” typically refers to materials that are between 1-100 nanometers, although the definition is still being debated (some say it should include materials up to 300 nanometers). Currently, there are several hundred “nanosilver” products on the market, and this number is expected to continue to rise in coming years.

becoming even more popular with the occurrence of various pathogen outbreaks (E. coli, swine flu, etc)(Silver 2003).⁶

Colloidal silver,⁷ a popular and easily available over-the-counter “natural health” or “folk” remedy that can include silver in nanoparticle size-ranges, was used throughout the 19th and 20th centuries as a treatment for a variety of colds and other ailments, and its use is skyrocketing in recent years. In the 1990s, there was a resurgence in the popular use of silver compounds as “immune system stimulants” and to treat diabetes, chronic fatigue syndrome, allergies and cancer, cardiovascular conditions, and numerous other conditions.

Beyond medical and health-related uses, there are countless other uses of different forms of silver currently. Silver has long been used in dental amalgams, along with mercury, and is used in jewelry and acupuncture needles, photography, batteries, cloud seeding, cement, swimming pools and hot tubs, mirrors, electronics, and more (Drake and Hazelwood 2005). Photography was the single largest use of silver for some time, although silver use in photography is decreasing because of the switch to digital photography. The advent and growth in the ability to create and use silver in nano-sized form—in which it has unique properties that make it useful for an even wider range of applications—are facilitating the increased use of silver in numerous fields.⁸

Is silver toxic to mammals?

Silver can exist in a variety of forms, including metallic silver (Ag^0), three cationic states (Ag^+ , Ag^{2+} , Ag^{3+}), a variety of silver salts and silver complexes, and colloidal forms.⁹ Recently, intentionally engineered nano-particulate forms are increasingly prevalent. The form of silver affects its level of toxicity and its fate and transport in the body and environment.¹⁰

Environmentally, ionic silver is considered the second most toxic metal after mercury because it can cause harm to prokaryotic and non-mammalian organisms at relatively low levels when it is bioavailable to them (Eisler 1996; Ratte 1999; Luoma 2008). Silver ions have a strong tendency to bind to sulfhydryl, amino, carboxyl, phosphate and imidazole groups that are found in

⁶ For example, see websites: http://www.silvergen.com/cancer_and_silver.htm, <http://testimonials.silvermedicine.org/cancer.php>, http://www.new-cancer-treatments.org/Cancer/DMSO_CS.html.

⁷ Colloidal silver is a liquid suspension of silver particles in a range of sizes, from nanometer to micrometer.

⁸ See the Silver Institute: http://www.silverinstitute.org/news_current.php

⁹ Silver compounds include silver proteins, silver nitrate, silver sulfide, silver chloride, silver arsephenamine, silver sulfadiazine, silver lactate, silver acetate, and more.

¹⁰ I do not review the environmental effects of silver (effects on bacteria, fish, other non-human organisms, its fate and transport in the environment, etc.) in this paper. For a thorough review of these issues, see Luoma (2008): http://www.nanotechproject.org/process/assets/files/7036/nano_pen_15_final.pdf

enzymes, proteins, DNA, and RNA. It can induce oxidation reactions and mimic ions that play essential roles in many organisms, such as sodium, calcium, and copper ions, thereby affecting the transport of these ions (Fung and Bowen 1996; Hollinger 1996; Luoma 2008). Silver ions can interfere with numerous functions critical to many organisms—e.g., disrupting enzymes on cell membranes or cell walls that are responsible for critical cell functions such as cell respiration and electron transport across membranes. Reflecting this, silver is an effective antibacterial because the ions induce oxidative stress at bacteria's cell wall, reducing the bacterial cells' ability to respire and maintain ion balance—thereby killing the cells. Silver ions are also highly toxic to fish because they perturb ion regulation in the gills by disrupting membrane transport of sodium (Luoma 2008).

While silver is considered very toxic environmentally because of the potent effects of ionic silver on non-mammalian cells and organisms, it is commonly described in the scientific literature as being harmless to mammalian organisms, including humans, except at very high doses (Petering 1976; Luckey and Venugopal 1979; Danscher 1981; Fung and Bowen 1996). Numerous experimental studies, however, suggest that silver can affect mammalian cells in many of the same ways it affects non-mammalians at a range of doses, and in recent years several articles and reviews on silver have suggested that silver's assumed low risk to mammals be re-evaluated (Hollinger 1996; Poon and Burd 2004; Luoma 2008)—especially given the increasing use of silver for a variety of applications.

A whirlwind tour of experimental studies

The intent of this review is not to critically assess or compare these studies, or to outline details, but to provide a very broad sense of what scientists have reported related to the toxicity of silver to mammalian cells and organisms in experimental studies. First, I briefly list some *in vitro* findings on silver toxicity in Table 1. Many studies listed here are from existing reviews on silver, including Hollinger (1996), Drake and Hazelwood (2005) and Lansdown (2007). I also did searches of historical and more recent literatures on silver.

In sum, many experimental studies demonstrate that, as in non-mammalian cells, in mammalian cells silver can bind, interact, and interfere with DNA, proteins and enzymes, affect membrane ion transport and membrane integrity, cause oxidative stress and cytotoxicity, significant immune responses, and more. These effects are usually attributed to silver ions—either directly or via release of ions from other silver compounds (Hollinger, 1996). It has been documented for some time that silver ions can significantly affect the mitochondrial electron transport chain in

mammalian cells, leading to a cascade of events and eventually cell death (Chappell and Perry 1954; Almofti, Ichikawa et al. 2003).

Table 1: In vitro studies using different forms of silver

Approximate doses (if reported) ¹¹	Type of cells studied	Effects	Reference
Silver ion			
Not available	Mitochondria isolated from rabbit cerebral cortex	↑ mitochondrial respiration	(Chappell and Perry 1954)
0.1ppm ¹²	Human epithelial cells	↑ death rate of cells Inhibition of cell growth	(Helgeland and Leirskar 1972), (Leirskar 1974)
1-10 μM	Human synovial cells	↓ collagen synthesis, ↓ protein synthesis, ↓ DNA synthesis, ↓ DNA content, ↓ synovial cell proliferation	(Goldberg, Kaplan et al. 1983)
Range of doses	Human and nonhuman mammalian cells	Binds and interacts with DNA, causes DNA strand breaks, disrupts DNA replication	U.S. ATSDR (1990) ¹³
Range of doses (specifics not available)	Rat hepatocyte	Enzyme leakage, loss of intracellular potassium	(Liu, Kershaw et al. 1991)
5-15 μM Effects seen as low as 1 μM	Human polymorphonuclear leukocytes	Production of superoxide anions	(Jansenn and Harms-Ringdahl 1993)
LC50s: -51 μM (T) -546 μM (B) -46 μM (monocytes) 24 hr exposures	Human lymphocytes, monocytes	Cytotoxicity to T and B lymphocytes and monocytes ¹⁴	(Steffensen, Mesna et al. 1994)
0.33 mM	Human basophils	Dose-dependent induction of histamine release, cellular toxicity	(Schedle, Samorapoompichit et al. 1988)
At 10 μM,	Rat mitochondria	Mitochondrial swelling,	Almofti (2003)

¹¹ In some cases doses are not clear or reported dose levels are missing critical information. Levels reported here are general levels/ranges of levels in which negative effects were seen.

¹² These studies examined silver released from dental amalgam materials; specific doses are unavailable, but this level was reported in a paper that cited Leirskar (1974).

¹³ United States Agency for Toxic Substances and Disease Registry, ATSDR (1990), see: <http://www.atsdr.cdc.gov/phs/phs.asp?id=537&tid=97>

¹⁴ This study found that the cytotoxicity of silver approximated that of mercury and it was more toxic than lead.

respiration reduced, at 100 μM , respiration completely inhibited		acceleration of respiration, opening of inner membrane pores, release of apoptogenic cytochrome c	
1-10 μM ¹⁵	Human neuron PC12 cells	Impaired protein & DNA synthesis, \uparrow oxidative stress, \downarrow cellular viability ¹⁶	(Powers, Wrench et al. 2010)
100% cell death at 5 $\mu\text{g/ml}$ (“aged” particles)	Human mesenchymal stem cells	Cell death (“aged” Ag particles had lethal conc. 20 X lower than freshly-prepared silver particles)	(Kittler, Greulich et al. 2010) ¹⁷
Silver nitrate and/or lactate			
30-70 μM	Rat hepatocytes (Ag nitrate & lactate)	\downarrow glutathione, \uparrow lipid peroxidation, loss of cell viability	(Baldi, Minoia et al. 1988)
100% suppression observed down to .0001% dilution of clinical conc. (.5%) of cream	Human leukocytes (Ag nitrate)	Severe inhibition of neutrophil and lymphocyte respiratory burst activity, mitogen-stimulated lymphocyte proliferation	(Zapata-Sirvent and Hansbrough 1993)
IC ₅₀ —30 μM For inhibition of lymphocytes IC ₅₀ —10 ⁻⁸ M for inhibition of Na, K-ATPase	Human lymphocytes (Ag nitrate)	\downarrow cell survival and cell viability, inhibition of Na, K ATPase	(Hussain, Anner et al. 1992)
.0007-.0055%	Human fibroblasts and keratinocytes (Ag nitrate)	\uparrow cytotoxicity	(Poon and Burd 2004)
20 μM : \uparrow death rate of cells 40, or 80 μM : coag. necrosis, rapid cell death	Mouse peritoneal macrophages (Ag lactate)	\uparrow coagulation necrosis and \uparrow cell death	(Rungby, Hultman et al. 1987)
Silver sulphadiazine			
100% cell death in 0.03, 0.05% Ag sulphadiazine	Human dermal fibroblasts	\downarrow cell proliferation, \uparrow cytotoxicity	(McCauley, Linares et al. 1989)

¹⁵ Interestingly, 1 μM silver ions enhanced cell numbers by suppressing ongoing cell death and impaired differentiation for both neurotransmitter types tested.

¹⁶ DNA synthesis was inhibited more by exposure to 10 μM silver ions than by exposure to 50 μM chlorpyrifos. Longer exposures reduced cell viability further and when DNA synthesis was inhibited further with onset of cell differentiation.

¹⁷ This study examined silver nanoparticles, but was included because it specifically assessed the effects of silver ions. See later discussion reviewing effects of engineered silver nanomaterials.

conc. After 48 hrs exposure			
1% silver sulfadiazine cream after 1 day	Human epidermal keratinocytes and fibroblasts	↓ cell proliferation, ↑ cytotoxicity	(Kuroyanagi, Kim et al. 1991)
0.001-0.004% of clinical concentration (1% silver sulfadiazine)	Human leukocytes (Ag nitrate)	Severe inhibition of neutrophil and lymphocyte respiratory burst activity, mitogen-stimulated lymphocyte proliferation	(Zapata-Sirvent and Hansbrough 1993)
1, 5, 10 µg /ml, significantly reduced cell survival; 1 wk @ 25 ug/mL, no colonies left	Human, mouse bone marrow cells	↓ colony count, ↓ leukocytes, granulocytes	(Gamelli, Paxton et al. 1993)

* The Agency for Toxic Substances & Disease Registry report cites the following studies showing that silver interacts with and affects DNA: Goff and Powers 1975; Loeb et al. 1977; Luk et al. 1975; Mauss et al. 1980; Robison et al. 1982; Scicchitano and Pegg 1987

In vivo (or isolated tissue) studies

Studies have documented that silver deposits in numerous organs of animals and humans after exposures, including: liver and kidneys (Ham and Tange 1972; Day, Hunt et al. 1976; Hultman, Enestrom et al. 1994; Berry, Dennebouy et al. 1995; Saeki, Nakajima et al. 2001; Pelkonen, Heinonen-Tanski et al. 2003), cardiovascular tissues (Olcott 1948; Lukanov and Atmadjov 1979; Jackson and Duling 1983; Kraft, Hansis et al. 2000; Pelkonen, Heinonen-Tanski et al. 2003), neurological tissues (Lansdown, 2007; Pelkonen et al., 2003), and numerous other organs (Pelkonen et al., 2003). The levels reported in animal and human organs and tissues, however, vary, probably because of animals analyzed, differences in how and when they were analyzed, what organs were analyzed, etc. For example, Humphreys and Routledge reported that the silver levels in human corpses were, from highest to lowest: skin, liver, adrenals, brain, thyroid, caecum, ovary and trachea. Pelkonen et al (2003) reported that mice given 0.03 mg/L of silver nitrate in drinking water for 1-2 weeks accumulated silver in the following order: musculus soleus, cerebellum, spleen, duodenum, and myocardial tissue. While silver has been shown to be able to cross the placental barrier and enter fetuses in animals, including humans (Reinhardt, Geldmacher et al. 1971; Danscher 1981; Rungby and Danscher 1983; Hanson, Donley et al. 2001; Saeki, Nakajima et al.

2001; Lyon, Patriarca et al. 2002), there is disagreement in the literature about whether or not it can cross the blood-brain barrier in animals.¹⁸

Many of the effects described in experimental studies in Table 1 are classic mechanisms of toxicity (and parallel the mechanisms of other known toxins, especially metals) and could feasibly result in tissue and organ damage in whole animals. In *vivo* studies, summarized in Table 2, are somewhat sparse, but indicate that silver can cause a number of detrimental effects in mammals at a variety of levels—including kidney and liver effects, effects on cardiovascular and muscle tissues, inflammation and immune system effects, neurological, reproductive/developmental, hemopoietic, and carcinogenic effects.

Table 2: In vivo (or isolated tissue) studies

Silver types/doses ¹⁹	Specific tissue and/or animal studied	Effects	Reference
Various effects (very old animal studies)			
A range of doses	Dogs, horses, guinea pigs, rabbits (given intravenous or subcutaneous injections of various types of silver, primarily metallic silver)	Death, leucopenia, bone marrow hyperplasia, anemia, blood sugar changes, edema of the lungs, gastrointestinal “catarrh,” nausea, loss of appetite, kidney effects (see below), central nervous system effects (see below)	(Hill and Pillsbury 1939) ²⁰
Kidney and/or Liver			
Silver thioglycerin-sodium sulfonate	Rabbit kidneys	Congestion, swelling of tubular epithelium, glomerular necrosis	(Vallery-Radot and Pasteur 1936)
Silver acetate, 130-1000 ppm in drinking water ²¹	Rat livers	Liver necrosis	(Bunyan, T. et al. 1968)

¹⁸ Lansdown (2007) concludes that silver’s ability to cross the blood-brain barrier in animals is uncertain. However, he cites Russian studies by the Joint FAO/WHO Expert Committee on Food Additives, suggesting that can cross the blood-brain barrier (Karchenko et al., 1972; Barkov & Piner, 1968), and an extensive series of rat studies suggest that silver ions can penetrate the blood brain barrier and spread heterogeneously throughout the central nervous system and concentrate there (Danscher et al., 1986; Stoltenberg et al., 1994; Freidheim et al., 1983; Takeuchi et al., 1989; Rungby & Danscher, 1983; Rungby, 1986; Rungby et al., 1987; Rungby 1990; Thorlacius-Ussing & Rungby, 1984). Van Breemen and Clemente (1955) found rats administered silver nitrate in drinking water over 6 to 8 months had silver deposition in the choroid plexus, area postrema, medulla, cerebrum, and cerebellum. Pelkonen (2003) found rats that ingested relatively low levels of silver ions in drinking water for two weeks accumulated silver in many organs, with the cerebellum accumulating the second highest amount.

¹⁹ In some cases details (included relevant aspects of doses) are not entirely clear or are absent, so they are not reported.

²⁰ Studies cited by Hill & Pillsbury on effects in animals included: Archard & Weil (1907); Brown (1915); Charcot et al. (1867); Petijean (1800-1900); Ribadeau et al. (1908); Schouse and Whipple (1931); Voigt (1926).

Silver acetate, 130-1000 ppm in food or 1500 ppm in drinking water	Livers of vitamin E-deficient weaning rats	Fatal liver necrosis by day 14	(Grasso, R. et al. 1969); see also (Grasso, Abraham et al. 1970)
Silver acetate, 0.5% in feed for 4 weeks	Pig livers	Liver lesions and necrosis, selenium-vitamin E deficiency	(Van Vleet 1976) ²²
Silver lactate, 20 mg/kg injections	Mouse kidneys & livers	↑ Lipid peroxidation	(Rungby and Ernest 1992)
Silver ion, 20 mg/kg	Rat and mouse livers	↑ Lipid peroxidation	(Shinogi and Maeizume 1993)
Silver nitrate, single subcutaneous injection, 10 mg/kg	Mice livers & serum	Silver-metallothionein complexes in liver, ↓ ceruloplasmin concentration, ↓ Cu concentration in serum	(Sugawara and Sugawara 1984)
Silver nitrate, single intravenous injection, 0.183 mg/kg	Rat serum	↓ ceruloplasmin oxidase activity and ↓ CU concentrations in serum	(Blaha, Havrdova et al. 1987)
.4 mg/ml silver lactate injection	Mouse livers	↑ Lipid peroxidation	(Rungby, Hultman et al. 1987)
Cardiovascular/muscle			
Silver nitrate or silver chloride, 1:1000 in sodium thiosulfate	Rats	Enlargement of the left ventricle of the heart ²³	(Olcott 1948)
Silver acetate, 0.15% in drinking water	Chicks	Exudative diathesis ²⁴ in pectoral region, peritoneal and pericardial spaces	(Bunyan, T. et al. 1968)
Silver nitrate, 900 ppm in food for first four weeks of life,	Turkeys	Grossly enlarged hearts, dilatation of right ventricle, 6 of 21	(Peterson, Jensen et al. 1973)

²¹ Selenium protected against damage at 130 ppm but not at 1000 ppm (see footnote #22). Vitamin E also protects against liver damage from silver.

²² Like some other toxic metals (arsenic, mercury, cadmium, thallium), silver is well known to interact with selenium and cause “lesions of selenium deficiency” in a variety of animals. According to Van Vleet (1976), these lesions included “massive hepatic necrosis in rats, exudative diathesis in chicks, and gizzard and cardiac myopathy in turkeys” (p. 1415) at lower levels of exposure than those needed to produce effects in pigs. Van Vleet cites Bunyan et al. (1968), Diplock et al. (1967), Grasso et al. (1968), Wagner et al., (1975) and several more. Van Vleet and other researchers speculate that silver's interactions with selenium prevent the forming or functioning of glutathione peroxidase (a critical cellular antioxidant that contains selenium).

²³ Olcott speculates that the heart enlargement is due to vascular hypertension, in turn due to deposition of silver that produced thickening of the basement membranes of the renal glomeruli.

²⁴ Exudative diathesis is severe edema of subcutaneous tissues; associated with Vitamin E deficiency.

then normal diet		turkeys died	
Silver acetate, 0.5% in feed for 4 weeks	Pig hearts	Fibrinoid necrosis of arterioles and small muscular arteries ²⁵	(Van Vleet 1976)
Silver metal, silver chloride electrodes, 2 hour exposure	Smooth muscle of isolated hamster cheek pouch arterioles	Lost all responsiveness to vasoactive stimuli ²⁶	(Lukanov and Atmadjov 1979; Jackson and Duling 1983) Lukanov and Atmadjov (1970)—similar results w/guinea pigs.
Inflammation/Immune			
Silver sulfadiazine, 1% topical cream	Mice	↓ leukocyte counts and ↓ nucleated bone marrow cells	(Gamelli, Paxton et al. 1993)
Silver nitrate, 0.01% or 0.05% in drinking water	Mice	Induction of serum antinucleolar antifibrillar autoantibodies; ↑ in renal, mesangial IgM deposits ²⁷ ;	(Hultman, Enestrom et al. 1994)
Metallic silver implants in striated muscle tissue	Hamsters	Persistent activation of leukocytes, disruption of microvascular endothelial integrity, massive leukocyte extravasation, venular dilation	(Kraft, Hansis et al. 2000)
Reproductive/developmental			
Silver nitrate, 0.04 mM/kg	Rats (adult)	Shrinkage, edema, and deformation of the epididymal tubules	(Hoey 1966)
Silver nitrate, 1% intrauterine injection	Monkeys (female adults)	Vaginal bleeding and pregnancy termination	(Dubin, Parmley et al. 1981)
Silver lactate, s.c. injections postnally, .10mg (1 st wk), .20 mg (2 nd wk), .35 mg (3-4 th wks)	Rats (newborn)	Smaller pyramidal cell layer in hippocampus, smaller body weights	Rungby, Slomianka et al. (1987) ²⁸

²⁵ These effects were also found in kidneys, stomach, and intestines.

²⁶ Authors speculated that these effects were due to silver ion's inhibition of the calcium pump. cardiac nerve supply. Convulsions may or may not be noted before respiratory embarrassment occurs.

²⁷ This study concluded that "silver seems to be a more specific inducer of anti-nucleolar/anti-fibrillar autoantibodies than mercury and gold" (p. 285); the highest deposits of silver were found in the kidney

²⁸ Authors speculate that this is due to lipid peroxidation resulting in "unstable intracellular membranes" (p. 267).

Silver chloride, 50 mg/day	Rats (mothers and fetuses)	Eliminated copper-containing ceruloplasmin from the mother rats' blood, caused developmental abnormalities and/or death in their embryos	(Shavlovski, Chebotar et al. 1995)
Central nervous system/neurological			
Injections of various forms and amounts of inorganic silver	Cats, dogs, horses, rabbits, guinea pigs	Central nervous system effects, eventual death ³	Numerous studies cited in Hill & Pillsbury (1939), p. 44-45 ^{3,29}
Silver lactate: - 0.5 mg I.P. injection (two) -0.015 % in drinking water for 125 days	Mice	Hypoactive behaviors	(Rungby and Danscher 1984)
Silver lactate, s.c. injections postnally, .10mg (1 st wk), .20 mg (2 nd wk), .35 mg (3-4 th wks)	Rats (newborn)	Smaller pyramidal cell layer in hippocampus, smaller body weights	Rungby, Slomianka et al. (1987)
Carcinoma			
Subcutaneous imbedding of silver foil	Rats	Fibrosarcomas	(Oppenheimer, Oppenheimer et al. 1956)
Injection of colloidal silver	Rats	Tumorigenesis	(Schmahl and Steinhoff 1960)

Argyria--the human body's mechanism to detoxify silver?

Despite experimental studies suggesting that silver can have toxic effects in mammalian cells and organisms, statements throughout scientific literatures indicate that silver is toxicologically innocuous to humans even when deposited in human tissues. The reason usually given for why it is harmless is that it is believed bind to cellular molecules and deposits outside the functioning cells of human organs (Fung and Bowen 1996; Drake and Hazelwood 2005). In humans, these silver deposits can eventually cause argyria, the permanent discoloration of the skin

²⁹ Hill and Pillsbury (1939) cite several studies dating back to the mid-1800s in which various kinds of animals were given injections of inorganic silver compounds resulting in central nervous system effects. Studies they cited included: Ball (1865); Charcot et al. (1867); Curci (1886); Cushny (1928) and Kraemer (1845); Meyers (1922); McGuigan (no date given); Orfila (1852); Rouget (1873). Based on these studies, Hill and Pillsbury concluded that the chief effects of inorganic silver compounds given intravenously are on the central nervous system, resulting in "... weakness, rigidity of the legs and resultant contractures, loss of voluntary movements and interference with the cardiac nerve supply. Convulsions may or may not be noted before respiratory embarrassment occurs. Sensation and reflex movements may persist after respiration ceases and the motor nerves are excitable even after death" (p. 45).

(blue-gray) and/or the related condition argyrosis, discoloration of the conjunctiva and cornea (Drake and Hazelwood, 2005; Hill & Pillsbury, 1939). Argyria and argyrosis are irreversible, but are described in the literature as only cosmetic conditions. The deposits that cause argyria are assumed to be inactive toxicologically—indeed, numerous papers state that the deposition of silver that causes argyria is a key mechanism by which the human body “detoxifies” silver (Hill and Pillsbury 1939; Drake and Hazelwood 2005).

There still seems to be considerable uncertainty about the exact mechanism by which argyric conditions occur, but it is thought that light triggers the photoreduction of silver compounds to form metallic silver, which is then oxidized by tissue and bound as silver sulfide, silver selenide, or other silver complexes (Danscher 1981; Berry, Dennebouy et al. 1995). These silver deposits in subcutaneous tissue and mucous membranes are thought to lead to enhanced melanin production and hence the blue-gray coloration, especially in areas exposed to the sun (Armitage, White et al. 1996; Drake and Hazelwood 2005; Silver, Phung et al. 2006). Studies suggest that argyria and argyrosis primarily result from exposure to soluble and/or ionic forms of silver (versus metallic forms), which are more readily taken up into the body than metallic and insoluble silver forms (Hill and Pillsbury 1939; Brooks 1981; Rosenman, Seixas et al. 1986; Drake and Hazelwood 2005).

Hundreds of cases of argyria and/or argyrosis have been documented in the last few centuries, most related to medicinal uses of silver and/or occupational exposures. Between 1802 and 1951, according to an FDA report, 365 cases of argyria were reported in the medical literature (Food and Drug Administration 1973.) Argyria cases were documented throughout the 1900s, and even though argyria is commonly thought to be a condition of the past, cases are still documented throughout a variety of medical and health literatures to this day. Numerous argyria cases have been reported in recent literatures associated with colloidal silver, nanosilver and/or other silver compounds (Schlotzer-Schrehardt, Holbach et al. 2001; Hori, Martin et al. 2002; White, Powell et al. 2003; Tomi, Kranke et al. 2004; Drake and Hazelwood 2005; Baker, Federico et al. 2007; Pala, Fronterre et al. 2008; Kim, Suh et al. 2009; Mayr, Kim et al. 2009). In 2002, a group of medical experts at the Washington Poison Center titled an article “Believe it or Not—Silver Still Poisons!” after reviewing five cases of people who took colloidal silver and developed argyria (Hori, Martin et al. 2002).

Does Silver Cause Human Health Effects Beyond Argyria? A Review of the Case Study Literature

Scattered throughout historical, scientific and popular literatures are numerous reports suggesting that silver exposures may cause negative health effects beyond argyria. The 1825 *Materia Medica* entry (Hahnemann) lists numerous adverse symptoms reported by several doctors in patients given silver nitrate or metallic silver in homeopathic medicines, including reports of: vertigo, gastrointestinal problems, severe pain throughout the head, various neurological symptoms (“stupid and hollow in the head”, “a kind of intoxication”), and more. The symptoms of argyria listed in the 1905 *Materia Medica* include “gastrointestinal catarrh, tissue wasting, uremia, albuminuria, fatty degeneration of the liver, kidney and heart, hemorrhages, fluidity of the blood, a grey color along the gum margins, skin and mucous membranes, paralysis, loss of coordination, convulsions, and death by paralysis of respiration” (Potter 1905).

Statements throughout more recent scientific and clinical literatures also question the assumption that silver is innocuous to humans. For example, after completing and publishing eight animal-based toxicological studies on silver, with a focus on neurological effects, (Rungby 1990) concludes: “The work discussed here suggests that exposure to silver may, in a number of circumstances, have pathological consequences” (p. 447). After examining a patient with eye damage related to silver exposure 35 years previously, (Schlotzer-Schrehardt, Holbach et al. 2001) concluded: “The tissue effects and cellular responses to silver accumulation are still unclear and debatable. Although the metal generally causes no clinical symptoms, its potential toxic effects should not be ignored” (p. 557). Similarly, (Poon and Burd 2004) noted that “The burns surgical community has perhaps overlooked the cytotoxic effects of silver... This study confirmed the antiproliferative effects of metal ions and speculated about the effects, whether cells were actually killed or unable to divide or both” (p. 140) and (Baker, Federico et al. 2007) note that “Current medical literature... suggests that colloidal silver ingestion is a dangerous therapy... and thus has no role in appropriate medical care” (p. 734).

In recent years, the uses of silver and nanosilver materials in water treatment are increasing. A few scientists have questioned the silver levels allowed as disinfectants in drinking water treatment—in the past (Barkov and El Piner 1968) and more recently (Pelkonen, Heinonen-Tanski et al. 2003). Pelkonen et al., for example, found accumulation of silver from drinking water in the cerebellum and musculus soleus (and several other tissues) in mice—at levels significantly lower (0.03 mg/l) than the levels allowed by WHO in drinking water (0.1 mg/l). These authors noted that the cerebellum plays a major role in co-ordinated muscle activity, and cited Rungby and Danscher (1984), who found that 0.015% silver nitrate in drinking water of mice for 125 days resulted in

hypoactivity, as well as other studies associating silver exposures with muscle paralysis (Sudmann, Vik et al. 1994; Iwasaki, Yoshimura et al. 1997). Based on these studies, they proposed that silver used in water treatment might affect humans' motor functions in areas where it is used and suggested that the existing WHO standards on the use of silver salts for disinfection of drinking water be re-evaluated.

Human health effects after silver exposures

The increasing popularity and use of silver and nanosilver in a wide range of products will result in both direct and indirect human exposures to it in many forms and sizes, potentially significantly above background levels for some sources.³⁰ Most (though not all) scientists agree that silver is not an essential element in the human body. Lansdown (2007), for example, says that silver “is not an acknowledged trace element in the human body and fulfills no physiological or biochemical role in any tissue even though it interacts with several essential elements...” (Lansdown 2007)(p. 237).³¹ However, there are many inconsistencies in the literature regarding silver's fate in the human body, suggesting that that is not very well understood. These inconsistencies notwithstanding, scientists agree that silver levels in the human body are very low unless a person is exposed to a silver source.³²

Not unexpectedly, the most commonly documented health effects related to human silver exposures are argyria and/or argyrosis (Drake and Hazelwood 2005). However, most clinicians have treated these conditions as purely cosmetic and therefore have not explored other health effects that may have been associated with them over the short or long term. Because of the abundance of papers describing argyria already in the literature, I focus only on *non-argyria* health effects related to silver exposures that have been documented in research and clinical studies.

Kidney and Liver Effects. As in animals, kidney and liver are known to be primary sites of silver deposition in humans after exposures. Silver deposits in the kidneys of exposed people have been demonstrated since at least the 1800s. One researcher (Mayr, Kim et al. 2009) noted recently that the “standard” argyric human glomerulus was beautifully illustrated by Jahn in 1894, and a 1905

³⁰ Silver levels in the environment are typically extremely low unless there is another source beyond natural sources (Luoma, 2008).

³¹ Some entities promoting silver for various health conditions, however, claim that people suffer from “the novel and undefined condition of ‘silver deficiency’” Lansdown, A. B. G. (2007). "Critical Observations on the Neurotoxicity of Silver." *Critical Reviews in Toxicology* 37(3): 237-250.p. S10).

³² Fate and transport of silver in the human body are not discussed in this paper; for a more thorough discussion, see ATSDR (1990).

medical text listed “fatty degeneration of the liver, kidney, and heart...” as symptoms of argyria (Potter 1905). In 1947, Olcott wrote that in many cases of argyria described “the lesions of the kidneys are among the most advanced changes found in any organ” (p. 813), (Olcott 1947) and 1971 medical text lists silver as a nephrotoxin (Beeson and McDermott 1973).

Unfortunately, however, very few studies have explored kidney and/or liver effects beyond documenting silver deposits in these organs and/or perhaps exploring minimal signs of kidney/liver detriments. Clinical studies of argyria patients contain sporadic mentions of kidney and liver related detriments (Maitre, Jaber et al. 2002; Chaby, Viseux et al. 2005; Mayr, Kim et al. 2009). One recent case study of an argyric patient with decreased kidney function (Mayr et al., 2009) was titled “Argyria and Decreased Kidney Function: Are Silver Compounds Toxic to the Kidney?” Another case describes an argyria patient who came to doctors with mild cardiac failure (and later died of bronchopneumonia) and also had abnormal liver function and an enlarged liver with lesions (Prescott and Wells 1994).

According to a book on the toxicology of metals (Goyer 1991) high exposures to silver in the workplace and/or medicines have been associated lesions of the kidneys. One of the workplace studies reviewed in this paper found evidence of decrements in kidney function among some workers (Rosenman, Moss et al. 1979). Humphrey and Routledge’s 1998 review of silver nitrate poisoning cases includes six cases involving patients who were administered silver nitrate in the urinary tract and/or bladder by medical professionals, resulting in inflammation in these tissues, kidney and intestinal damage (Jerkins, Noe et al. 1986; Vijan, Keating et al. 1988; Anon 1990), and calcification and argyria in the urinary tract (Raghavaiah and Soloway 1977; Kojima, Uchida et al. 1993).³³

Cardiovascular effects. Paralleling animal studies, silver is known to build up in human cardiovascular tissues. The famous Barnum and Bailey “Blue Man” was autopsied after death and his heart was found to be “distinctly increased in size” and “markedly distended” on one side; the authors noted “silvery blue tints” in many of the cardiovascular tissues (Gettler, Rhoads et al. 1927).

Scattered case reports throughout history suggest that buildup of silver in cardiovascular tissues could be associated with adverse effects. Goyer (1991) noted that high exposures to silver in the workplace and/or medicines have been associated with arteriosclerosis (Goyer 1991). Mentions of arteriosclerosis are found throughout clinical and case study literatures. One case (Dietl, Anzil et

³³ As these Humphreys and Routledge note, however, some of the damage is likely due to nitrate forms of silver, which are very caustic.

al. 1984) described the body of a woman who died at age 59 after taking regular doses of silver nitrate. Autopsy revealed silver deposition in heart muscle, marked arteriosclerosis of coronary arteries, and rupture of low thoracic aorta. A man who came in with symptoms of mild cardiac failure, rapidly deteriorated and then died of bronchopneumonia, was found to have silver deposits throughout his skin and other organs, scarring of the anteroseptal left ventricular wall, and his “right coronary artery was completely occluded by atheroma” (Prescott and Wells 1994)(p. 556). (Archer 2008) describes a case of left bundle branch block and a dilated, nonhypertrophic cardiomyopathy in a patient who had been ingesting colloidal silver and gold. Anecdotally, one argyria victim, who became famous as the modern-day “Blue Man” after he was featured on ABC News in 2008, was quoted in 2009 in an online news story, at age 58, saying he had colon cancer and had to have stints in his arteries to deal with blocked arteries.³⁴

Interestingly, there have been cases of silver implants being associated with cardiovascular problems. Silzone heart valves, which had silver coatings intended to reduce risks of infective endocarditis, were eventually taken off the market because of thrombo-embolytic complications, including deaths (Lansdown 2007).³⁵ Meanwhile, silver is currently promoted online as a potential treatment for cardiovascular problems. For example, a 2010 issue of The Silver Institute’s “Silver News” describes findings of a study (Shrivastava, Bera et al. 2009) suggesting that nanosilver particles are highly effective as anticoagulants—that they “significantly reduced adhesion of platelets to vessel walls and subsequent clogging of the vascular system” (p. 1, Silver Institute, 2010).³⁶

Respiratory Effects. Inhalation of soluble silver compounds, primarily in workplace settings, has been associated with respiratory tract irritation, emphysema, and reduction of pulmonary volume, silver “staining” of alveoli and bronchial tissue, and lesions of the lung (McLaughlin, Barrie et al. 1945; Barrie and Harding 1947; Perrone, Clonfero et al. 1977; Rosenman, Moss et al. 1979; Brooks 1981; Forycki, Zegarski et al. 1983; Rosenman, Seixas et al. 1986; Goyer 1991; Drake and Hazelwood 2005).

³⁴ See: <http://www.mid-day.com/news/2009/sep/110909-Paul-Karason-argyria-permanent-blue-FDA.htm> (accessed August 24, 2010)

³⁵ This recall was later rescinded (it’s not clear why). See: <http://www.mhra.gov.uk/Publications/Safetywarnings/MedicalDeviceAlerts/Advicenotices/CON008871> (accessed August 24, 2010)

³⁶ The Silver Institute: <http://www.silverinstitute.org/images/pdfs/1q2010.pdf>. Notably, the newsletter also reported that the study showed that nanosilver “significantly retarded the loss of phosphorous...and reduced the loss of calcium from bones” and that it “had the added value of providing antibacterial action and does not collect in the body because it is systematically eliminated by the liver and kidneys”(p. 1).

McLaughlin et al (1945) reported serious lung effects in four men who died after working as silver finishers for decades and thus being exposed to silver and oxide dusts. The authors concluded that “inhaled silver dust obviously has a great affinity for the elastica of the alveolar walls and the smaller pulmonary vessels...” (p. 228). However, these reports were based on autopsies and lacked any (or only crude) measurements of silver levels in the workplace.

Decades after these studies, Rosenman et al. (1979, 1987) did clinical field studies on small number of workers in industries that created and handled various silver compounds. In the first study, they examined 30 workers exposed to silver nitrate and silver oxides, they found that “the majority of workers at the plant complained of both eye and upper (nose and throat) and lower (cough, wheezing and chest tightness), respiratory tract irritation,” and those who reported these symptoms had them every day (p. 431). Bronchoscopy revealed silver deposition in the bronchi and some squamous metaplasia, and seven men had evidence of pulmonary obstruction (but five of these were or ex-smokers).

In a later study, Rosenman et al. (1987) examined workers in a factory that manufactured silver and several other precious metal powders and had air silver levels over the OSHA standard at the time. They found that most workers had elevated blood and urine silver levels, and 15 of 27 examined workers complained of upper respiratory symptoms and 9 complained of lower respiratory symptoms. Forycki et al., (1983) describe a worker exposed for 4 hours to “massive vapours” of high purity metallic silver (of unknown amount) after which he developed severe head pain and respiratory distress. The patient was treated for several days and eventually recovered. These researchers conclude that this case refutes the assumption that silver is non-toxic and “clearly points at the potential danger of toxic action of silver on the body” (p. 199).

Unfortunately, significant data gaps in these workplace studies make it difficult to draw clear connections between silver exposures and health effects. In all workplaces studied, people were exposed to a number of other potential toxins, exposures were not clearly measured (or not measured at all), tissues were not adequately analyzed, and numerous other limitations.

Reproductive/Developmental Effects. Silver has been explored at various times for use as an abortifacient and/or sterilizing agent (as an alternative to surgery) (Ringrose 1973; Dubin, Parmley et al. 1981). In an experiment to test methods for office procedures for female sterilization, Ringrose (1973) injected silver nitrate paste into the uterus of 200 women, which resulted in successful sterilization of the majority of the women due to “obliterative fibrotic reactions at the corneal end of

the oviduct” and “endometrial alterations” that “discouraged subsequent successful nidation” (p. 151). Ringrose concluded that “the procedure is well tolerated, simple, economical and results in diminished menstrual flow. It appears to be particularly suitable for use in underdeveloped nations without sophisticated operative facilities as well as in our own society where burgeoning medical costs dictate the avoidance of hospitalization expenses whenever possible” (p. 151).

There are a few case reports showing that silver can transfer from mother to fetus. In one case, a pregnant woman was fatally intoxicated with silver nitrate. Autopsy showed silver in the liver, lung, and muscle tissue of the fetus (Reinhardt, Geldmacher et al. 1971; Rungby and Danscher 1983). In a short analysis of the livers of human fetuses that were aborted (therapeutically or spontaneously), born prematurely (and later died), or anencephalic, (Robkin, Swanson et al. 1973) found high levels of silver and mercury in fetal livers of anencephalic fetal livers compared to aborted fetuses. More recently, Lyon et al. (2002) analyzed 157 neonates (aged <1 day to 6 years) and found silver concentrations that significantly exceeded the levels typically found in older children and adults. They speculated that silver from mother’s mercury-silver dental amalgams is inherited by the fetus during pregnancy/lactation from mothers with dental amalgams, concluding that “silver can cross the placental barrier and may accumulate in liver during the third trimester of pregnancy by the same mechanisms as for copper” (p. 1038).

Finally, one case-control epidemiological study (not focused on silver specifically) found a statistically significant association between maternal exposures to some trace elements in drinking water and developmental anomalies (Aschengrau, Zierler et al. 1993). These researchers examined 1,039 congenital anomaly cases, 77 stillbirth cases, 55 neonatal death cases, and 1,177 controls. They gathered trace element levels from routine analyses of public water supplies in the communities in which the women resided during pregnancy. Their analyses found that the frequency of major malformations was associated with increased detectable silver levels. The highest level of silver detected in any water tested for the study (0.0013 mg/l) was orders of magnitude less than the current U.S. EPA drinking water standard for silver (0.1 mg/L).³⁷

Immune system: Delayed wound healing and leucopenia have been documented in burn and wound patients treated with silver and/or nanosilver compounds (Hollinger 1996)—likely reflecting silver ions’ negative effects on cell proliferation and immune cells demonstrated in experimental studies

³⁷ Water supplies in the communities tested tended to be acidic, which would make silver more soluble and bioavailable. Also, interestingly, the effects of silver were not seen with high sodium levels (perhaps reflecting silver ions known ability to mimic sodium?)

(McCauley, Linares et al. 1989; Kuroyanagi, Kim et al. 1991; Gamelli, Paxton et al. 1993; Jansenn and Harms-Ringdahl 1993; Burd, Kwok et al. 2007). Many of these researchers, based on their findings, strongly urged caution in the use of silver and/or nanosilver-based wound dressings.

Ocular Effects. The eye is one of the organs where silver tends to deposit, and in addition to numerous cases of ocular argyria (argyrosis), decreased night vision and ocular burns have been reported among many silver workers (Moss, Sugar et al. 1979; Rosenman, Moss et al. 1979; Rosenman, Seixas et al. 1986). In many of these studies, effects were significantly associated with elevated silver levels in the urine and/or blood and deposits of silver throughout the body. (Schlotzer-Schrehardt, Holbach et al. 2001) found intracellular accumulation of silver in stromal keratocytes, along with cell damage and necrosis, and visual impairment in a man exposed to an explosion of glass equipment containing silver 35 years previously.

Neurological Effects. Comments throughout older as well as recent literatures suggest that silver may have neurological effects in humans. For example, in 1984, Rungby and Danscher noted that “cases have been presented in which argyria patients have exhibited a diversity of symptoms: paralysis, convulsions, ataxia, disturbances of coordination and frontally located EEG responses” (p. 398)(Rungby and Danscher 1984).³⁸ A later clinical study (Ohbo, Fukuzako et al. 1996) describes a case of seizures caused by chronic exposure to silver medications and cites a study finding abnormal electroencephalographic and brain scan findings in a argyria patient (Rosenblatt and Cymet 1987). The National Institutes of Health National Center for Complementary and Alternative Medicine’s website states that beyond argyria “...side effects from using colloidal silver products may include neurologic problems (such as seizures)...”³⁹

There have been numerous cases in which silver has been documented in neurological tissues of people exposed to it (Lansdown 2007). Lansdown’s 2007 review of the neurological effects of silver describes a case (Dietl, Anzil et al. 1984) of a woman who self-administered silver nitrate for an ulceration of the tongue for years. Following an intense period of sunning, she developed severe argyria and manic depressive psychosis, and eventually died of a ruptured aortic aneurysm at age 65. Autopsy revealed silver deposits in many organs, including central nervous system tissues, and progressive glial changes and cellular gliosis in many areas of the brain. The

³⁸ These authors cite Dreisbach 1974, Franken & Langhof 1964, Reinhardt et al. 1971, Rosenman et al. 1979, Aaseth et al., 1981.

³⁹ <http://nccam.nih.gov/health/silver/>, accessed 7-20-10

authors of this case study also found evidence that silver can enter brain cells, paralleling several previous studies (they cite Hori & Miyazawa, 1977; Putzke, 1967; Reymond et al., 1980; Scott & Norman, 1980).

Lansdown (2007) describes another case study on a patient who used a silver nitrate stick for 9 years for oral mycosis, and eventually developed progressive hypogeusia, hyposmia, vertigo, gait disturbance, skin hypesthesia, and weakness—which the researchers attributed to deposition of insoluble silver sulfide throughout many neurological tissues (Westhofen and Schafer 1986). Chemosensory and electrophysiological studies confirmed the diagnoses of neurological impairment, and analyses of tissues revealed silver deposits in many neurological tissues (Fung and Bowen 1996) p. 5). Studies show that silver can also enter neurological tissues after people use over-the-counter silver nasal treatments, which have been on the market for a very long time (Goebel and Muller 1973; Landas, Fischer et al. 1985; Landas, Bonsib et al. 1986). Landas et al (1985) found silver throughout the brain tissues of a woman who had taken silver nose drops for years, and speculated that this could reflect axonal transport of silver from sites outside of the blood-brain barrier.

There are a few notable recent cases of neurological effects related to chronic colloidal silver intake for various health problems. One clinical research paper describes the case of a 71-year-old man who developed myoclonic status epilepticus and then went into a coma after taking colloidal silver to self-treat prostate cancer. After a prolonged coma, he entered a “persistent vegetative state” and eventually died of pneumonia, 5.5 months after his seizures first began. Autopsy revealed “microscopic evidence of diffuse Alzheimer type 2 astrocytosis and microglial activation” and silver in the gray matter of the cerebrum (Mirsattari, Hammond et al. 2004)p. 1409). Also, EEG analyses revealed toxic encephalopathy. Although the patient had cancer, and had been taking several herbal remedies as well as local radiotherapy, the authors concluded based that his epilepticus, coma, and vegetative state were due to silver neurotoxicity rather than these or other potential causes they considered. In another case, a 58-year-old man who regularly ingested homemade silver colloid and sprayed it on his face. He was eventually admitted to the hospital with neurological damage, including “intracerebral hemorrhage with contralateral plegia, hypethesia, and hemineglect and right-sided nervus abducens palsy” as well as high blood pressure, decreased kidney function and argyria (Mayr, Kim et al. 2009).

Silver nitrate and other silver compounds, widely used in burn and other medical treatments, have resulted in many cases of argyria and have been connected with neurological issues in a few

cases (Lansdown 2007). (Iwasaki, Yoshimura et al. 1997) describe a case in which a severe burn patient with end-stage renal disease was treated with silver sulphadiazine. Within five days of being started on this treatment, his mental status deteriorated. Serum silver concentration was markedly increased and he eventually went into a coma and died after several months. Autopsy revealed high deposition of silver in the brain even though silver treatment had been discontinued for some time before the patient's death. The authors proposed that silver can affect neurological function in patients with kidney disorders because the kidneys cannot efficiently remove silver from serum.

Though Lansdown says there is only limited evidence to show silver burn treatments cause neurological damage, he raises caution about the increasingly extensive use and incorporation of silver in medical devices implanted over the long-term. He describes a case, also described by others (Vik, Andersen et al. 1985; Sudmann, Vik et al. 1994) in which a woman became unstable and exhibited muscle weakness in her leg five years after insertion of a prosthesis with silver cement—noting that this case provides “strong evidence implicating silver as a cause of neurological toxicity and behavioral changes derives from use of as silver as an antimicrobial agent in arthroplasty cement” (p. 245). Lansdown concludes that all medical uses of silver will release silver ion under the likely conditions of use and that this silver will be absorbed into the body, enter the bloodstream and deposit in soft tissues including neurological tissues.

Cancer. While silver compounds are commonly promoted online as cancer treatments,⁴⁰ and at the same time called highly carcinogenic by other online commentators,⁴¹ I did not locate any studies on human silver exposures and cancer for this review. The 1990 Agency for Toxic Substances & Disease Registry (ATSDR) report cites several *in vitro* studies showing that silver ions bind with DNA and interfere with replication. However, the report notes that “Animal toxicity and human occupational studies using normal routes of exposure have not provided indications of carcinogenicity” and then concludes that “silver is not expected to be carcinogenic in humans” (p. 38)(ATSDR 1990). A 2009 document on the toxicity of ionic silver classifies silver in category D for carcinogenicity, which means “no data available” (Morrow 2009).

⁴⁰ See: <http://testimonials.silvermedicine.org/silvergen-leukemia-silver.php>, http://www.new-cancer-treatments.org/Cancer/DMSO_CS.html, http://findarticles.com/p/articles/mi_m0ISW/is_274/ai_n16359688/ and more. (accessed August 24, 2010).

⁴¹ This online health consultant states that “for more than 40 years we have known that silver is a hard, proven carcinogen—a cancer causing agent. Metallic silver is listed in the 1979 Registry of Toxic Effects as causing cancer in animals”—see: <http://www.cqs.com/silver.htm> (accessed Aug. 23, 2010).

Deaths. In addition to those mentioned above, there are many deaths related to silver in the literatures, with wide ranging (and in many cases unknown or only roughly estimated) lethal doses. A 2000 European Commission risk assessment document on the use of silver in medicines states that “therapeutic IV administration of 50 mg or more is lethal, provoking pulmonary edema, hemorrhage, and necrosis of the bone marrow, liver, and kidneys” (p. 6) (Commission 2000) (Fowler and Nordberg 1986). Several cases described in Humphreys & Routledge’s review of poisoning cases involving silver nitrate described cases in which people died after exposures to a range of doses (Humphreys and Routledge 1998). It is not always clear whether these deaths were related to silver use, since in some cases victims had health conditions that could lead to death and it is very difficult to ascertain how much silver they were exposed to (although in some cases doses are known). For example, Lansdown (2007) describes a case of a woman who was given 7 grams of silver nitrate to induce abortion, and died within three hours (as did her fetus). Autopsy revealed silver widely distributed throughout her body, including her brain (Reinhardt, Geldmacher et al. 1971). A 60 year-old man developed argyria and extremely high skin and plasma silver levels after exposure to silver nitrate dressings for 8 hours daily for 30 days, and he eventually died. An 18 year-old man died after receiving silver nitrate for 6 days.

Other effects. Humphreys & Routledge (1998) reviewed hundreds of case studies of people who were purposely or accidentally exposed to silver nitrate in a variety of contexts (in a range of amounts), both short and long-term. Effects described in these cases (other than argyria) that were not described above include: eye/vision damage, chemical burns, cyanosis, blood pressure changes, nausea, and more. Other individual studies on exposures to various silver compounds mention a range of effects not discussed above, such as high blood pressure and various allergic responses (rashes, irritated eyes, sneezing, sore throat and stuffy nose) (Rosenman, Seixas et al. 1986; Rosenman, Seixas et al. 1987; Drake and Hazelwood 2005). “Abdominal pain” and other types of gastro-intestinal disturbances (peritonitis) have also been mentioned in many papers (McLaughlin, Barrie et al. 1945; Marshall and Schneider 1977; Rosenman, Moss et al. 1979; Rosenman, Seixas et al. 1986; Drake and Hazelwood 2005).

A June 2009 EPA background document for the re-registration of silver and silver compounds as pesticides notes that “a search of the OPP Incident Data System (IDS) found 52 silver incidents” related to the use of silver-based Brita water filters. Symptoms reported included rash, hives, severe itching, bloating and stomach problems, diarrhea, dizziness, raised blood

pressure, edema, constant kidney pain, urinary tract and kidney infection, sore throat, and a dry mouth. The document notes that “it is difficult to clearly link the incidents to the silver used in the filter as the incident data was not complete. Levels of silver (if any) were not measured, and there is no known medical history of people who reported the incidents” (p. 38) (ATSDR 1990)

Discussion

This broad review of a wide array of studies—even with the many substantial limitations and gaps—suggests that silver can have negative human health effects beyond cosmetic effects. If nothing else, taken together, these studies strongly suggest that silver’s oft-cited “harmlessness” to humans is far from certain. Indeed, experimental studies on animals outlined here suggest that silver—primarily via silver ions released from it—can cause several effects classically associated with known toxins, such as interacting with key cellular proteins and essential ions, binding with DNA/RNA and inhibiting synthesis, and invoking oxidative stress and cytotoxicity—similar to those caused by other toxic heavy metals such as mercury (National Research Council, 2000; (Council 2000; Powers, Wrench et al. 2010). Interestingly, mercury, which like silver was used as a medicinal and in numerous products before researchers clearly documented its toxicity to humans, is thought to cause toxicity via mechanisms similar to those described above for silver—such as interfering with glutathione, disrupting protein synthesis, causing mitochondrial damage, and increasing oxidative stress and lipid peroxidation (National Research Council, 2000, p. 55).

It is commonly argued in risk assessment that lab-based experimental studies that dose small numbers of animals with high levels of the material of interest have limited value in predicting human effects, and that *in vitro* studies have even less relevance to living animals and/or humans (although this approach is changing more recently in favor of cell-culture system, cell-free, and computer-modeling methods, etc). Of course, it is not ethical to experiment on humans; this is one key reason cell culture and animal studies have been developed to test chemicals for safety. In this case, however, people have been directly exposed to silver in a myriad of ways for a very long time—so we have in essence unplanned, uncontrolled human experiments. Among human studies that mention effects other than argyria, patterns in health outcomes parallel those that might be expected given findings of toxic effects in cell and animal studies, such as kidney, neurological, immune and cardiovascular effects.

Unfortunately, as already articulated, none of the people in the clinical studies described were followed over the long-term to attempt to better understand these and other effects, types and

levels of silver they were exposed to, to more carefully control for other exposures that could have caused effects, or to detect sub-clinical or clinical effects, etc. Are silver deposits in tissues actually inert as believed—or do these deposits slowly release silver ions over time that then circulate in the body, causing harm? Numerous studies cited in this paper, in fact, indicate that silver does not simply deposit in one place and remain inert there permanently.

If people who took silver regularly over long periods of time eventually developed kidney or liver deficits, or other subclinical health problems, these effects—and silver exposures potentially connected to them—would not be documented unless somebody was carefully tracking them and publishing their findings, or unless people were reporting these effects and connecting them to silver exposures. If people exposed to silver chronically developed neurological deficits, particularly subclinical effects such as memory or IQ deficits or other difficult to identify neurological changes, or their children who were exposed as fetuses developed neurobehavioral problems, these patterns are not likely to be detected without carefully planned long-term epidemiological studies. These effects are also not necessarily going to be reported by those who experience them, or connected to past silver exposures by them or their doctors.⁴²

Silver Studies Raise Many Red Flags, Despite Data Gaps

Despite the red flags studies reviewed here raise about silver's potential harm to humans, there are still many gaps in the studies that make it challenging to clearly elucidate silver's effects on human health—especially over the long term. It is puzzling that, given these red flags and gaps, so many scientists, medical and health professionals, and risk assessors seem to have concluded with some certainty that silver is harmless to humans other than argyria. It is also odd that more research hasn't been done to fill these gaps—research that would be valuable in evaluating the risks of nanosilver.

The silver literature lacks clear information on dose-response relationships, even for argyria. An extremely wide range of silver levels (including relatively low levels) and many different types of silver have been associated with argyric effects. Hill and Pillsbury (1939), still cited as a basis for government risk assessments and standards on silver to this day, noted that “the effect of the rate of administration of silver compounds is not known; there is no evidence indicating that the giving of *extremely small amounts of silver* over a prolonged period in any way lessens the danger of argyria from any given amount of a silver compound” (p. 128, emphasis added). They later

⁴² Several studies have noted that argyria patients have been reluctant to report their silver usage and in some cases people who clearly had argyria could not recall or denied knowledge of exposures to any silver at all.

conclude: “It is rather surprising that, considering the wide vogue which colloidal silver has had in the treatment of nasal and upper respiratory infection, no studies have been done which afford answers as to whether, first, what proportion of silver applied actually enters the gastro-intestinal or respiratory tract; and second, how much of the silver is absorbed and permanently retained in the body” (p. 130). They end the book by recommending that physicians and pharmacists be educated on the dangers of argyria, warning labels be placed on silver medications, and further studies be done on the “rate of retention of silver under conditions of ordinary clinical use” (p. 131).

These recommendations have apparently not been taken very seriously by researchers. Over 70 years after the Hill & Pillsbury review was written, scientific understanding of silver’s transport, fate and/or accumulation in the human body has not developed much further and there is relatively little information on health outcomes from human exposures to silver beyond argyria. Clear information about silver exposure levels in human case studies is lacking, making it difficult to draw conclusions about their relevance—even for argyria outcomes (not to mention other potential health outcomes). The 1990 ATSDR summary of the health effects of silver notes that even for argyria cases “only rough estimates of the amount of silver ingested were located, and therefore precise levels of exposure resulting in discoloration cannot be established” (p. 19). The report concluded that “in general, quantitative data were nonexistent or unreliable and could not be used to establish LOAELs” for silver and argyria outcomes.

There is even less information about health effects other than argyria in people chronically exposed to silver. The majority of clinical studies are very limited—most done after people had been exposed to silver for some time and developed argyria and/or died. Most of these individuals were not examined until their health conditions were well-advanced (or after death), and many were exposed to other potentially toxic compounds and a variety of other confounding factors. For post-mortem cases, researchers often had only autopsy data with little or no exposure information. No studies tracked the subsequent health over the long term of the individuals who chronically consumed silver and developed argyria or argyrosis but didn’t die. Other than one case-control drinking water study described (which was not focused on silver), no epidemiological studies on silver were located. Although there have been a few studies in workplaces that handle silver, they are relatively short-term, methodologically limited on a number of levels, and nearly all focused on argyria-related outcomes.

In sum, research on chronic and subclinical effects of silver are warranted given findings in past studies and its increasing uses in recent decades (Hollinger 1996). Some have stressed, in

particular, the need for more research on silver's neurological effects. Lansdown (2007), for example, argued that more attention to silver in neurological tissues "is highly relevant now in view of the greatly increased use of silver in medical devices, major technological advances in materials science, and the widespread applications of nanotechnology in medicine" (Lansdown, p. 238). A 2010 study, moreover, raised concerns about the long-term neurological effects of silver given experimental findings suggesting that silver shares the same targets shared by many developmental neurotoxicants, such as mercury (Powers et al., 2010).

Nanosilver: New challenges or just more silver ions?⁴³

Complicating questions about silver's safety for humans, a plethora of new consumer and industrial products on the market are claiming to include "nanosilver," or silver particles in the nanometer size range. These uses are expected to increase human and environmental exposures to silver in both nano and non-nano forms. Moreover, many scientists have warned that nanosilver may pose new and unique risks compared to larger forms of silver (Hollinger 1996; Lansdown 2007; Luoma 2008; Wijnhoven, Peijnenburg et al. 2009).⁴⁴

Though they are often overlooked in discussions about nanosilver, some of the literatures reviewed in this paper on the safety of "non-nano" silver are pertinent to these debates. Colloidal silver, which has been on the market since at least the late 1800s, includes varied proportions of nanometer-sized particles. So, case studies reviewed in this paper on colloidal silver are studies on nano-sized silver particles, although they are likely mixed with larger sizes of silver.⁴⁵ Moreover, there is fairly solid scientific consensus that silver ions, which are *smaller* than nanoparticles (about .1nm), are the most toxic forms of silver. Silver ions can be released from all forms and sizes of silver, including nanosilver, in certain conditions. Indeed, nanoparticulate forms of silver are likely to release more ions per surface area, because of their higher surface-to-volume ratio, and scientists

⁴³ This paper will only briefly touch on recent studies related to engineered nanosilver. Numerous reports (Luoma, 2008, Wijnhoven et al., 2009, Ahamed et al., 2010, and more) have comprehensively reviewed potential health and environmental issues related to nanomaterials and/or nanosilver, so we will not review them at length here. At the time of the writing of this paper, there were hundreds of research studies on nanosilver, and the number was increasing almost weekly. These and newer studies on nanosilver are also listed here: <http://www.nanoceo.net/nanorisks/silver-particles>.

⁴⁴ As discussed earlier, Luoma has thoroughly reviewed the environmental implications of silver and nanosilver and they will not be reviewed here.

⁴⁵ Also, regardless of the form of silver the organism are exposed to, this silver can be transformed into nano-sized forms in the body: e.g., one study located in this review noted the presence of nano-sized silver granules (also containing other metals) in tissues of people with argyria—e.g., Lansdown (2007, p. 242; see also Bleehan et al. 1981).

speculate that this could make them more potent in cells and the human body (Lansdown 2007; Lubick 2008; Luoma 2008; Wijnhoven, Peijnenburg et al. 2009).

In other words, silver ions are silver ions, whether released from nanosilver or larger forms. The growing body of recent studies on the toxicity of nano forms of silver reveal effects in a range of cell types that largely parallel those found for other forms of silver, including: (1) binding with sulfhydryl groups, interaction with/disruption of proteins, RNA, DNA, glutathione, and other molecules that play critical roles in cells; (2) disrupting membrane transport processes and causing other significant membrane damage; (3) generating reactive oxygen species (oxidative stress), cell morphological changes, cytotoxicity, apoptosis and necrosis (Wijnhoven, Peijnenburg et al. 2009; Ahamed, AlSalhi et al. 2010). Many of these effects were shown with doses within the 1-200 $\mu\text{g/ml}$, and most doses were within the 5-50 $\mu\text{g/ml}$ range (Ahamed, AlSalhi et al. 2010).

In vivo studies on mammalian animals (rats, mice) to date have shown that nanosilver tends to deposit in liver, kidney, brain, lungs, and spleen and can cause effects in these organs—many similar to those caused by other forms of silver. Studies on rats and mice have shown liver and kidney damage (Cha, Hong et al. 2008; Cho, Lee et al. 2008; Sung, Ji et al. 2009), and inhalation studies have shown decreased tidal and minute volumes and inflammatory responses (Takenaka, Karg et al. 2001; Sung, Ji et al. 2009; Ahamed, AlSalhi et al. 2010). The liver and brain were target organs in rats after prolonged silver nanoparticle exposures via inhalation (Takenaka, Karg et al. 2001; Sung, Ji et al. 2009; Ahamed, AlSalhi et al. 2010). Another study showed that inhalation of silver nanoparticles caused changes in cerebrum and cerebellum genes, as well as genes associated with motor neuron disorder neurodegenerative disease, and immune cell function (Lee, Choi et al. 2009). Rhaman et al. showed that silver nanoparticles produced oxidative stress and altered gene expression in mouse brain after interperitoneal injections, which resulted in apoptosis and neurotoxicity (Rahman, Wang et al. 2009).

Paralleling mammalian studies, nanosilver's effects in a number of non-mammalian animals that are used as models for human health effects have been explored. Significant effects have been shown at relatively low levels ($\mu\text{g/ml}$ range). Studies on zebrafish, for example, have found the following effects from exposures to nanosilver at $\mu\text{g/ml}$ levels: oxidative stress, DNA damage, developmental and morphological abnormalities in embryos, hatching delays, increased mortality, pericardial edema and cardiac arrhythmias in embryos, and more (Lee, Nallathamby et al. 2007; Asharani, Wu et al. 2008; Bar-Illan, Albrecht et al. 2009; Park, Jongheop et al. 2010); studies on fruit flies, several species of fish, and oysters have shown induction of oxidative stress and/or

oxidative stress genes, DNA damage, apoptosis in larvae, retarded brain development, morphological malformations in embryos, reproductive failures, impaired tolerance to hypoxia, high mortality, and more (Chae, Pham et al. 2009; Ahamed, AlSalhi et al. 2010; Bilberg, Malte et al. 2010; Laban, Nies et al. 2010; Ringwood, McCarthy et al. 2010; Wise, Goodale et al. 2010; Wu, Zhou et al. 2010; Scown, Santos et al. 2010). Though not considered a mammalian model, a recent study showed that nanosilver induced stress and altered thyroid hormone in amphibians at very low levels—at or below acute toxicity levels and below the North American water quality guidelines (Hinther, Vawda et al. 2010). Several other studies on non-mammalian species have shown negative effects from nanosilver at very low levels—again, paralleling known effects of silver in other forms (again, see Luoma 2008 and studies listed on www.nanoceo.net).

Nanosilver's effects parallel those of bigger forms of silver--does nanosilver pose new and/or heightened risks?

It is notable that toxicity findings in recent studies on nanosilver—hundreds published to-date and more coming out almost weekly—generally parallel findings described in this paper from older studies on silver ions and various “non-nano” silver forms (albeit older studies used much more crude methods and recent studies much more sophisticated ones). Scientists propose that effects of nanosilver are due to the higher rate of release of silver ions because of the higher surface-to-volume ratios of nano-sized particulates (Luoma 2008; Wijnhoven, Peijnenburg et al. 2009; Kittler, Greulich et al. 2010). If the toxic effects of nanosilver are due to release of silver ions, it is not particularly surprising that nanosilver materials have similar toxic effects as other forms of silver.

That said, some scientists have proposed that nanoparticulate forms of silver may, in addition to releasing silver ions, may be able to release ions in more potent ways and also could have new and unique mechanisms of toxicity that go beyond the release of silver ions. For example, via endocytotic mechanisms in which cells can “engulf” nano-sized particles, nanosilver particles may be more able to enter eukaryotic cells than larger silver forms, where they could deliver silver ions in the form of a nanosilver particle to the interior of cells (Luoma, 2008). Indeed, silver nanoparticles have been found to be transported more easily into certain areas than silver ions, including the cytoplasm of cells (Sondi and Salopek-Sondi 2004; Elechiguerra, Burt et al. 2005; Morones, Elechiguerra et al. 2005; Pal, Tak et al. 2007; Shrivastava, Bera et al. 2007; Skebo 2007;

Raffi, Hussain et al. 2008), the cell nucleus (Asharani, Wu et al. 2008), and the brain (Takenaka, Karg et al. 2001; Ji, Jung et al. 2007; Cho, Lee et al. 2008; Sung, Ji et al. 2009).

Studies have also shown that nanosilver particles could carry heavy metals and other toxins into cells in a “Trojan horse-type mechanism” (Lubick 2008; Luoma 2008; Park, Jongheop et al. 2010). Further, once inside cells, nanosilver particles could continue to release silver ions for long periods of time, prolonging their toxicity inside the cell (Navarro, Piccapietra et al. 2008; Kittler, Greulich et al. 2010). Kittler et al. (2010), for example, found that the nanosilver particles slowly released silver ions over several weeks, becoming increasingly toxic to human mesenchymal cells. Supporting the proposal that nanoparticles can have distinct effects from ions alone, another study found that silver nanoparticles impaired neurodevelopment of PC12 cells (causing oxidative stress, impaired protein synthesis, impaired cell differentiation) in ways that were clearly distinct from those of Ag⁺ alone and dependent on size and coating (Powers, Badireddy et al. 2010).

Nano forms of silver can be incorporated more readily into materials than other forms

On a more practical level, nanosilver materials can be more easily incorporated into a wide variety of materials and products than larger forms of silver—and therefore are being incorporated into numerous consumer products and industrial materials that couldn’t incorporate silver previously. Silver in a wide variety of forms will eventually be released from these materials as they are used and discarded. Workers in industries where these products are created and handled are particularly vulnerable to potential health effects from nanosilver exposures, given that aerosolized nanosilver particles are emitted in workplaces that handle them (Old and Methner 2008; Tsai, Ada et al. 2009) and can be easily inhaled--depositing in lung tissues and causing inflammation and eventually disease (Tsai, Ada et al. 2009; Ahamed, AlSalhi et al. 2010; Li, Muralikrishnan et al. 2010; Quadros and Marr 2010). Nanoparticles can also enter the brain through the nasopharygeal system (Ahamed, AlSalhi et al. 2010). Consumers who use these products could be exposed via inhalation, ingestion, and dermal exposures. Nanosilver materials could access human reproductive systems via contraceptive devices and feminine hygiene products on the market that are incorporating nanosilver (Ahamed, AlSalhi et al. 2010). In other words, in sum, given the ubiquitous use of nanosilver materials in commerce, human exposures will be—and likely already are—common and widespread.

Conclusions

This review of human-health related studies on silver suggests that the assumption that silver is completely innocuous to humans and other mammals is not based on sufficient evidence—and, that it overlooks a considerable amount of evidence to the contrary. Unfortunately, this may be a dangerous assumption because it has clearly encouraged the widespread use of silver and nanosilver in countless consumer products and the purposeful ingestion of silver compounds for nearly every health problem imaginable. The assumption of silver's safety to humans has been uncritically accepted and used by silver industries and others to market nanosilver all over the world for a huge range of applications. Moreover, many risk assessors and regulatory agencies in the United States, it seems, have also accepted this assumption with little exploration of the wide range of available literatures on silver and the significant data gaps that need to be filled before assuming that silver is safe for humans (Morrow 2009).

Why have there been so few systematic studies on silver's effects on humans—particularly longer-term, subclinical effects such as neurological deficits? Rungby and Danscher (1983), speculate that silver has received little attention because its toxicity was assumed to be low and it was also assumed that it couldn't cross the blood-brain barrier. Numerous studies reviewed here, of course, refute both assumptions.

There are also several deeper and more pervasive socio-cultural, economic, and political reasons for the reluctance to explore silver's toxicity to humans. Silver has been viewed for thousands of years as a “magical” substance with powerful healing properties. It has played a central role in advancing human civilization and later in the industrial revolution, and was among the key reasons for the rapid colonialization of the New World by Europeans.⁴⁶ Moreover, there are significant profits—to mining companies, numerous industries, medicine, and consumer product manufacturers—involved with the wide range of uses for silver and nanosilver. A google search of silver and/or nanosilver readily reveals the ways these entities have been aggressively marketing silver compounds as necessary, beneficial and safe all over the world. Further, because it has been used for so many millennia as an antimicrobial, and is still used widely, there is likely considerable reluctance on the part of health and medical communities to scrutinize it carefully. And, adding an odd twist to the social and cultural dynamics of silver promotion, silver also has passionate proponents among alternative health communities, in part because it is easy to obtain, relatively inexpensive, and perceived to be a natural miraculous cure-all.

⁴⁶ See: http://www.silverinstitute.org/silver_history.php

Regardless of the reasons, the increasing use of silver and nanosilver will, directly or indirectly, result in increased human exposures to silver. Over time, silver materials in nano and non-nano forms will be emitted from workplaces, industries, consumer and other nanosilver products into air, water, soil, waste, sewage sludge, etc. Further, silver's negative effects on aquatic organisms and ecosystems at very low levels are well documented (Luoma 2008), and these effects reverberate through entire ecosystems in ways that will directly and indirectly affect humans as well. Ubiquitous uses of silver could also build up widespread microbial resistance to silver, potentially rendering it useless as an antimicrobial and adding to existing super-pathogen problems. Taken together, the studies reviewed in this paper suggest that increased silver levels have the potential to cause significant and negative effects on public and ecosystem health over the long term—effects that will be difficult, if not impossible, to reverse or mitigate.

Finally, this review raises ethical questions about science and policy decisions related to toxins, risk and human health. Countless scientists, NGOs, and others (including myself) have recommended that more studies be done on silver and nanosilver. Indeed, this review brings to light several unknowns about silver's and nanosilver's risks to humans that are primarily due to lack of appropriate studies. More studies—especially exposure studies, which are currently very sparse—would certainly improve risk assessments on silver and nanosilver.

Yet hundreds of studies have already been done on silver, dating back over a century, and hundreds of much more sophisticated studies have been done on nanosilver in recent years. Patterns in older silver studies suggest that silver has negative effects in cells and organisms quite similar to other toxic metals such as mercury. Moreover, though nanosilver might have some unique toxicological effects from “conventional” forms, studies already clearly show that it has toxic effects similar to other silver forms—and is very likely to be more toxic and potent than larger forms. Based on this review and the growing body of literature on nanosilver, I propose that enough is known already about the toxicity of silver as a metal to begin taking strong steps to prevent human exposures and environmental releases now, rather than waiting till silver becomes the next mercury.

References

- Ahamed, M., M. S. AlSalhi, et al. (2010). "Silver nanoparticle applications and human health." Clinica Chimica Acta Article in Press(DOI: 10.1016/j.cca.2010.08.016).
- Almofti, M. R., T. Ichikawa, et al. (2003). "Silver Ion Induces a Cyclosporine A-Insensitive Permeability Transition in Rat Liver Mitochondria and Release of Apoptogenic Cytochrome c." Journal of Biochemistry **134**: 43-49.
- Anon (1990). "Silver nitrate, duodenal damage, legal action." Clinical Alert **28**(1): 97-104.
- Archer, S. L. (2008). "Dilated cardiomyopathy and left bundle branch block associated with ingestion of colloidal gold and silver is reversed by British antiLewsite and vitamin E: The potential toxicity of metals used as health supplements." Canadian Journal of Cardiology **24**(5): 397-399.
- Armitage, S. A., M. A. White, et al. (1996). "The determination of silver in whole blood and its application to biological monitoring of occupationally exposed groups." Ann Occup Hyg **40**(3): 331-338.
- Aschengrau, A., S. Zierler, et al. (1993). "Quality of community drinking water and the occurrence of late adverse pregnancy outcomes." Archives of environmental health (USA).
- Asharani, P. V., Y. L. Wu, et al. (2008). "Toxicity of silver nanoparticles in zebrafish models." Nanotechnology **19**(25): 255102-255110.
- ATSDR (1990). Toxicological Profile for Silver. Agency for Toxic Substances & Disease Registry, U. S. Public Health Service.
- Baker, C., M. J. Federico, et al. (2007). "Case report: skin discoloration following administration of colloidal silver in cystic fibrosis." Current Opinions in Pediatrics **19**: 733-735.
- Baldi, C., C. Minoia, et al. (1988). "Effects of silver in isolated rat hepatocytes." Toxicology Letters **41**(3): 261.
- Bar-Illan, O., R. M. Albrecht, et al. (2009). "Toxicity assessments of multisized gold and silver nanoparticles in zebrafish embryos." Small **5**(16): 1897-1910.
- Barkov, G. D. and L. I. El Piner (1968). "The need for limiting the silver content of drinking water" Gigiena i sanitarii **33**: 16.
- Barrie, H. J. and H. E. Harding (1947). "Argyro-siderosis of the lungs in silver finishers." British Journal of Industrial Medicine **4**: 225-229.
- Beeson, P. B. and W. McDermott (1973). Cecil-Loeb Textbook of Medicine Philadelphia W. B. Saunders.
- Berry, J. P., R. Dennebouy, et al. (1995). "Scanning ion microscopy mapping of basement membrane elements and arterioles in the kidney after selenium-silver interaction." Cellular and Molecular Biology **41**(2): 265-270.
- Bilberg, K., H. Malte, et al. (2010). "Silver nanoparticles and silver nitrate cause respiratory stress in Eurasian perch (*Perca fluviatilis*)." Aquatic Toxicology **96**(2): 159-165.
- Blaha, K., J. Havrdova, et al. (1987). "The effect of ^{110m}Ag on ceruloplasmin oxidase activity in rats. ." Journal of Hygiene, Epidemiology, Microbiology, and Immunology **31**(1): 39-43.
- Brooks, S. M. (1981). "Lung disorders resulting from the inhalation of metals." Clinics in Chest Medicine **2**(2): 235-254.
- Bunyan, J., D. A. T., et al. (1968). "Vitamin E and stress: Nutritional effects of dietary stress with silver in vitamin E-deficient chicks and rats." British Journal of Nutrition **22**: 165.
- Burd, A., C. H. Kwok, et al. (2007). "A comparative study of the cytotoxicity of silver-based dressings in monolayer cell, tissue explant, and animal models." Wound Repair and Regeneration **15**(1): 94-104.

- Cha, K., H.-W. Hong, et al. (2008). "Comparison of acute responses of mice livers to short-term exposure to nano-sized or micro-sized silver particles." Biotechnology Letters **30**(11): 1893-1899.
- Chaby, G., V. Viseux, et al. (2005). "Topical silver sulfadiazine-induced acute renal failure." Ann Dermatol Venereol **132**: 891-893.
- Chae, Y. J., C. H. Pham, et al. (2009). "Evaluation of the toxic impact of silver nanoparticles on *Japanese medaka (Oryzias latipes)*." Aquatic Toxicology **94**: 320-327.
- Chappell, J. B. and S. V. Perry (1954). "Effect of silver ions on mitochondrial adenosine triphosphatase." Nature **174**: 930-931.
- Cho, A. A., W. S. Lee, et al. (2008). "Occupational generalized argyria after exposure to aerosolized silver." Journal of Dermatology **35**: 759-760.
- Commission, E. (2000). Opinion on Toxicological Data on Colouring Agents for Medicinal Products: E 174 Silver. S. C. o. M. P. a. M. Devices.
- Council, N. R. (2000). Toxicological Effects of Methylmercury. Washington, D. C. , National Academy Press.
- Dansch, G. (1981). "Light and electron microscopic localization of silver in biological tissue." Histochemistry **71**: 177-186.
- Day, W. A., J. S. Hunt, et al. (1976). "Silver deposition in mouse glomeruli." Pathology **8**: 201-204.
- Dietl, H. W., A. P. Anzil, et al. (1984). "Brain involvement in generalized argyria." Clinical Neuropathology **3**(1): 32-36.
- Drake, P. L. and K. J. Hazelwood (2005). "Exposure-Related Health Effects of Silver and Silver Compounds: A Review." Ann Occup Hyg **49**(7): 575-585.
- Dubin, N. H., T. H. Parmley, et al. (1981). "Effect of silver nitrate on pregnancy termination in cynomolgus monkeys " Fertility and Sterility **36**(1): 106-109.
- Eisler, R. (1996). Silver hazards to fish, wildlife, and invertebrates: A synoptic review. Contaminant Hazard Reviews, Pautuxent Wildlife Research Center, US Geological Survey. **Reston VA** 63 pp.
- Elechiguerra, J. L., J. L. Burt, et al. (2005). "Interaction of silver nanoparticles with HIV-1." Journal of nanobiotechnology **3**: 6-17.
- Food and Drug Administration, U. S. (1973.). D. M. Branch. Rockville, Maryland. **OTC Volume 100037-100039**.
- Forycki, Z., W. Zegarski, et al. (1983). "Acute silver poisoning through inhalation." Bulletin of the Institute of Maritime and Tropical Medicine in Gdynia **34**(3-4): 199-203.
- Fowler, B. A. and G. F. Nordberg (1986). Silver. Handbook on the toxicology of metals. L. Friberg, G. F. Nordberg and V. B. Vouk, Elsevier. **2**: 521-531.
- Fung, M. C. and D. L. Bowen (1996). "Silver products for medical indications: risk-benefit assessment." Clinical Toxicology **34**(1): 119-126.
- Gamelli, R., T. P. Paxton, et al. (1993). "Bone marrow toxicity by silver sulfadiazine." Surgery, Gynecology and Obstetrics **177**(2): 115-120.
- Gettler, A. O., C. P. Rhoads, et al. (1927). "A contribution to the pathology of generalized argyria with a discussion of the fate of silver in the human body." American Journal of Pathology: 631-651.
- Goebel, H. H. and J. Muller (1973). "Ultrastructural observations on silver deposition in the choroid plexus of a patient with argyria." Acta Neuropathology **26**: 247-251.
- Goldberg, R. L., S. R. Kaplan, et al. (1983). "Effect of heavy metals on human rheumatoid synovial cell proliferation and collagen synthesis." Biochemical Pharmacology **32**(18): 2763-2766.
- Goyer, R. A. (1991). Toxic effects of metals. Cassereit and Doull's Toxicology. M. Amdur, J. Doull and C. Klaasen, Pergamon Press 623-680.

- Grasso, P., R. Abraham, et al. (1970). "Hepatocellular necrosis from dietary silver in vitamin E-deficient rats. ." Journal of Pathology **100** ix.
- Grasso, P., A. R., et al. (1969). "the role of dietary silver in the production of liver necrosis in vitamin E-deficient rats." Experimental and Molecular Pathology **11**(2): 186-199.
- Ham, K. N. and J. D. Tange (1972). "Silver deposition in rat glomerular basement membrane." Aust. J. Biol. Med. Sci. **50**: 423-434.
- Hanson, S. R., S. A. Donley, et al. (2001). "Transport of silver in virgin and lactating rats and relation to copper." J. Trace Elem. Med. Biol. **15**: 243-253.
- Helgeland, K. and J. Leirskar (1972). "A further testing of the effect of dental materials on growth and adhesion of animal cells *in vitro*." European Journal of Oral Sciences **80**(1): 206-212.
- Hill, W. R. and D. M. Pillsbury (1939). Argyria: The Pharmacology of Silver. Baltimore, The Williams & Wilkins Company.
- Hinther, A., S. Vawda, et al. (2010). "Nanometals induce stress and alter thyroid hormone action in amphibians at or below North American water quality guidelines." Environmental Science & Technology Online ahead of print(DOE: 10.1021/es101902n).
- Hoey, M. J. (1966). "The effects of metallic salts on the histology and functioning of the rat testis." Journal of Reproduction and Fertility **12**: 461-471.
- Hollinger, M. A. (1996). "Toxicological aspects of topical silver pharmaceuticals." CRC Critical Reviews in Toxicology **26**(3): 255-260.
- Hori, K., T. G. Martin, et al. (2002). "Believe it or not--silver still poisons! ." Veterinary and Human Toxicology **44**(5): 291-292.
- Hultman, P., S. Enestrom, et al. (1994). "Selective induction of anti-fibrillar autoantibodies by silver nitrate in mice." Clinical and Experimental Immunology **96**: 285-291.
- Humphreys, S. D. M. and P. A. Routledge (1998). "The toxicology of silver nitrate." Adverse Drug Reactions & Toxicology Review **17**(2/3): 115-143.
- Hussain, S., R. M. Anner, et al. (1992). "Cystein protects Na, K-ATPase and isolated human lymphocytes from silver toxicity." Biochemical and Biophysical Research Communications **189**(3): 1444-1449.
- Iwasaki, S., A. Yoshimura, et al. (1997). "Elimination study of silver in a hemodialyzed burn patient treated with silver sulfadiazine cream." American Journal of Kidney Diseases **30**(2): 287-290.
- Jackson, W. F. and B. R. Duling (1983). "Toxic effects of silver-silver chloride electrodes on vascular smooth muscle." Circulation Research **53**(1): 105-108.
- Jansenn, G. and M. Harms-Ringdahl (1993). "Stimulating effects of mercuric and silver ions on the superoxide anion production in human polymorphonuclear leukocytes." Free Radical Research Communications **18**(2).
- Jerkins, G. R., H. M. Noe, et al. (1986). "An unusual complication of silver nitrate treatment of hemorrhagic cystitis: case report." Journal of Urology **136**: 456-458.
- Ji, J. H., J. H. Jung, et al. (2007). "Long-term stability characteristics of metal nanoparticle generator using small ceramic heater for inhalation toxicity studies." Inhalation Toxicology **19**(9): 745-751.
- Kim, Y., H. S. Suh, et al. (2009). "A case of generalized argyria after ingestion of colloidal silver solution " American Journal of Industrial Medicine **52**: 246-250.
- Kittler, S., C. Greulich, et al. (2010). "Toxicity of Silver Nanoparticles Increases during Storage Because of Slow Dissolution under Release of Silver Ions." Chemistry of Materials(22): 4548-4554.

- Kittler, S., C. Greulich, et al. (2010). "Toxicity of silver nanoparticles increases during storage because of slow dissolution under release of silver ions." Chemistry of Materials **22**(16): 4548-4554.
- Klasen, H. J. (2000). "Historical review of the use of silver in the treatment of burns." Burns **26**: 117-130.
- Kojima, Y., K. Uchida, et al. (1993). "Argyrosis of the urinary tract after silver nitrate instillation: report of a case." Hinyokika Kyo **39**: 41-44.
- Kraft, C. N., M. Hansis, et al. (2000). "Striated muscle microvascular response to silver implants: A comparative *in vivo* study with titanium and stainless steel." Silver Implants and Microcirculation 192-199.
- Kuroyanagi, Y., E. Kim, et al. (1991). "Evaluation of a silver wound dressing capable of releasing silver sulfadiazine." Journal of Burn Care & Rehabilitation **12**(2).
- Laban, G., L. F. Nies, et al. (2010). "The effects of silver nanoparticles on fathead minnow (*Pimephales promelas*) embryos." Ecotoxicology **19**(1): 185-195.
- Landas, S., S. M. Bonsib, et al. (1986). "Argyria: Microanalytic-morphologic correlation using paraffin-embedded tissue." Ultrastructural Pathology **10**(10).
- Landas, S., J. Fischer, et al. (1985). "Demonstration of regional blood-brain barrier permeability in human brain." Neuroscience Letters **57**: 251-256.
- Lansdown, A. B. G. (2007). "Critical Observations on the Neurotoxicity of Silver." Critical Reviews in Toxicology **37**(3): 237-250.
- Lee, J. H., Y. U. Choi, et al. (2009). "Genomics-based screening of differentially-expressed genes in the brains of mice exposed to silver-nanoparticles via inhalation " Journal of Nanoparticle Research Online ahead of print(doi: 10.1007/s11051-009-9666-2).
- Lee, K. J., P. D. Nallathamby, et al. (2007). "In Vivo Imaging of Transport and Biocompatibility of Single Silver Nanoparticles in Early Development of Zebrafish Embryos." ACS Nano **1**(2): 133-143.
- Leirskar, J. (1974). "On the mechanisms of cytotoxicity of silver and copper amalgams in a cell culture system." European Journal of Oral Sciences **82**: 74-81.
- Li, J. J. e., S. Muralikrishnan, et al. (2010). "Nanoparticle-induced pulmonary toxicity." Experimental Biology and Medicine **235**: 1025-1033.
- Liu, J., W. C. Kershaw, et al. (1991). "The protective effect of metallothionein on the toxicity of various metals in rat primary hepatocyte culture." Toxicology and Applied Pharmacology **107**(1): 27-34.
- Lubick, N. (2008). "Nanosilver toxicity: Ions, nanoparticles--or both? ." Environmental Science & Technology **42**(23): 8617.
- Luckey, T. D. and B. Venugopal (1979). Toxicity of Group I Metals Metal Toxicity in Mammals B. Venugopal and T. D. Luckey. New York, Plenum Press: 32-36.
- Lukanov, J. and P. Atmadjov (1979). "Investigating the effect of silver ions on the contractile function of smooth-muscle preparations from guinea pig stomach, *in vitro*." Folia Medica **21**: 11-19.
- Luoma, S. N. (2008). Silver Nanotechnologies and the Environment: Old problems or new challenges? Washington, DC, The Project on Emerging Nanotechnologies, Woodrow Wilson International Center for Scholars: 66.
- Lyon, T., D. B., M. Patriarca, et al. (2002). "Age dependence of potentially toxic elements (Sb, Cd, Pb, Ag) in paediatric subjects." Journal of Environmental Monitoring **4**: 1034-1039.
- Maitre, S., K. Jaber, et al. (2002). "Increased serum and urinary levels of silver during treatment with topical silver sulfadiazine." Ann Dermatol Venereol **129**: 217-219.

- Marshall, J. P. and R. P. Schneider (1977). "Systemic argyria secondary to topical silver nitrate." Archives of Dermatology **1077-1079**.
- Mayr, M., M. J. Kim, et al. (2009). "Argyria and decreased kidney function : Are silver compounds toxic to the kidney?" American Journal of Kidney Diseases **53(5)**: 890-894.
- McCauley, R. L., H. Linares, et al. (1989). "*In vitro* toxicity of topical antimicrobial agents to human fibroblasts." Journal of Surgical Research **46**: 267-274.
- McLaughlin, A. I. G., H. J. Barrie, et al. (1945). "Iron oxide dust and the lungs of silver finishers." The Lancet(March 17): 337-341.
- Mirsattari, S. M., R. R. Hammond, et al. (2004). "Myoclonic status epilepticus following repeated oral ingestion of colloidal silver." Neurology **62**: 1408-1410.
- Morones, J. R., J. L. Elechiguerra, et al. (2005). "The bactericidal effect of silver nanoparticles." Nanotechnology **16(10)**: 2346-2353.
- Morrow, M. (2009). Ionic Silver: Toxicity and Weight of the Evidence. United States Environmental Protection Agency. A. Division. United States Environmental Protection Agency.
- Moss, A., A. Sugar, et al. (1979). "The ocular manifestations and functional effects of occupational argyrosis." Archives of Ophthalmology **97**: 906-908.
- Navarro, E., F. Piccapietra, et al. (2008). "Toxicity of Silver Nanoparticles to *Chlamydomonas reinhardtii*." Environ Sci Technol **42(23)**: 8959-8964.
- Ohbo, Y., H. Fukuzako, et al. (1996). "Argyria and convulsive seizures caused by ingestion of silver in a patient with schizophrenia." Psychiatry and Clinical Neurosciences **50**: 89-90.
- Olcott, C. T. (1947). "Experimental argyrosis. IV. Morphologic changes in the experimental animal " American Journal of Pathology **24**: 813-833.
- Olcott, C. T. (1948). "Experimental argyrosis: V. hypertrophy of the left ventricle of the heart in rats ingesting silver salts." American Journal of Pathology **24**: 138-149.
- Old, L. and M. M. Methner (2008). "Engineering Case Reports: Effectiveness of local exhaust ventilation (LEV) in controlling engineered nanomaterial emissions during reactor cleanout operations." Journal of Occupational and Environmental Hygiene **5**: D63-D69.
- Oppenheimer, B., E. Oppenheimer, et al. (1956). "Carcinogenic effects of metals in rodents." Cancer Research **16**: 439-441.
- Pal, S., Y. K. Tak, et al. (2007). "Does the antibacterial activity of silver nanoparticles depend on the shape of the nanoparticle? A study of the Gram-negative bacterium *Escherichia coli*." Applied and Environmental Microbiology **73(6)**: 1712-1720.
- Pala, G., A. Fronterre, et al. (2008). "Ocular argyrosis in a silver craftsman " Journal of Occupational Health **50**: 521-524.
- Park, E.-J., Y. Jongheop, et al. (2010). "Silver nanoparticles induce cytotoxicity by a Trojan-horse type mechanism." Toxicology in Vitro **24**: 872-878.
- Pelkonen, K. H. O., H. Heinonen-Tanski, et al. (2003). "Accumulation of silver from drinking water into cerebellum and musculus soleus in mice." Toxicology **186(1-2)**: 151-157.
- Perrone, S., E. Clonfero, et al. (1977). "Observations on four cases of occupational argyrosis." Med Lav **68**: 178-186.
- Petering, H. G. (1976). "Pharmacology and toxicology of heavy metals: silver." Pharmacol. Ther. **A. 1**.
- Peterson, R. P., L. S. Jensen, et al. (1973). "Effect of silver-induced enlarged hearts during the first four weeks of life on subsequent performance of turkeys." Avian Diseases **17(4)**: 802-806.
- Poon, V. K. M. and A. Burd (2004). "In vitro cytotoxicity of silver: implication for clinical wound care." Burns **30**: 140-147.

- Potter, S. (1905). Compendium of Materia Medica; Therapeutics and Prescription Writing Philadelphia, P. Blakiston's Son & Co. .
- Powers, C. M., A. R. Badireddy, et al. (2010). "Silver nanoparticles compromise neurodevelopment in PC12 cells: Critical contributions of silver ion, particle size, coating and composition." Environmental Health Perspectives Online ahead of print(DOE: 10.10.1289/ehp.1002337).
- Powers, C. M., N. Wrench, et al. (2010). "Silver Impairs Neurodevelopment: Studies in PC12 Cells." Environmental Health Perspectives **118**(1): 73-79.
- Prescott, R. J. and S. Wells (1994). "Systemic Argyria." Journal of Clinical Pathology **47**: 556-557.
- Quadros, M. E. and L. C. Marr (2010). "Environmental and human health risks of aerosolized silver." Journal of Air & Waste Management **60**: 770-781.
- Raffi, M., F. Hussain, et al. (2008). "Antibacterial Characterization of Silver Nanoparticles against E. Coli ATCC-15224." J. Mater. Sci. Technol **24**(2): 192-196.
- Raghavaiah, N. V. and M. S. Soloway (1977). "Anuria following silver nitrate irrigation for intractable bladder hemorrhage." Journal of Urology **118**: 681-682.
- Rahman, M. F., J. Wang, et al. (2009). "Expression of genes related to oxidative stress in the mouse brain after exposure to silver-25 nanoparticles." Toxicology Letters **187**(1): 15-21.
- Ratte, H. T. (1999). "Bioaccumulation and toxicity of silver compounds: A review." Environmental Toxicology and Chemistry **18**(1): 89-108.
- Reinhardt, G., V. Geldmacher, et al. (1971). "Akute Todliche Vergiftung mit Silbernitrat als Folge eines Abtreibungsversuches." Arch Kriminol **148**: 69-78.
- Ringrose, C. A. D. (1973). "Office Tubal Sterilization." Obstetrics and Gynecology **42**(1): 151-155.
- Ringwood, A. H., M. McCarthy, et al. (2010). "The effects of silver nanoparticles on oyster embryos." Marine Environmental Research **69S1**: S49-S51.
- Robkin, M. A., D. R. Swanson, et al. (1973). "Trace metal concentrations in human fetal livers." Transactions of the American Nuclear Society **17**: 97.
- Rosenblatt, M. J. and T. C. Cymet (1987). "Argyria: Report of a case associated with abnormal electroencephalographic and brain scan findings." J. Am. Osteopath. Assoc. **87**: 509-512.
- Rosenman, K. D., A. Moss, et al. (1979). "Argyria: Clinical implications of exposure to silver nitrate and silver oxide." Journal of Occupational Medicine **21**(6): 430-435.
- Rosenman, K. D., N. Seixas, et al. (1986). "Potential nephrotoxic effects of exposure to silver." British Journal of Industrial Medicine **44**: 267-272.
- Rosenman, K. D., N. Seixas, et al. (1987). "Potential nephrotoxic effects of exposure to silver." British Journal of Industrial Medicine **44**: 267-272.
- Rungby, J. (1990). "An experimental study on silver in the nervous system and on aspects of its general cellular toxicity." Danish Medical Bulletin **37**(5): 442-449.
- Rungby, J. and G. Danscher (1983). "Neuronal accumulation of silver in brains of progeny from argyric rats." Acta Neuropathology(61): 258-262.
- Rungby, J. and G. Danscher (1984). "Hypoactivity in silver exposed rats." Acta Pharmacology and Toxicology **55**: 398-401.
- Rungby, J. and E. Ernest (1992). "Experimentally induced lipid peroxidation after exposure to chromium, mercury or silver: interactions with carbon tetrachloride." Pharmacology & Toxicology **70**(3): 205.
- Rungby, J., P. Hultman, et al. (1987). "Silver affects viability and structure of cultured mouse peritoneal macrophages and peroxidative capacity of whole mouse liver." Archives of Toxicology **59**: 408-412.
- Saeki, K., M. Nakajima, et al. (2001). "Accumulation of silver in the liver of three species of pinnipeds." Environmental Pollution **112**: 19-25.

- Schedle, A., P. Samorapoompichit, et al. (1988). "Metal ion-induced toxic histamine release from human basophils and mast cells." Journal of Biomedical Materials Research, Part A **39**(4): 560-567.
- Schlotzer-Schrehardt, U., L. M. Holbach, et al. (2001). "Multifocal corneal argyrosis after an explosion injury." Cornea **20**(5): 553-557.
- Schmahl, D. and D. Steinhoff (1960). "Experimental carcinogenesis in rats with colloidal silver and gold solutions." Z Krebsforsch **63**: 586-591.
- Scown, T. M., E. M. Santos, et al. (2010). "Effects of aqueous exposure to silver nanoparticles of different sizes in rainbow trout." Toxicological Sciences **115**(2): 521-534.
- Shavlovski, M. M., N. A. Chebotar, et al. (1995). "Embryotoxicity of silver ions is diminished by ceruloplasmin--further evidence for its role in the transport of copper." Biometals **8**: 122-128.
- Shinogi, M. and S. Maeizume (1993). "Effect of preinduction of metallothionein on tissue distribution of silver and hepatic lipid peroxidation." Biological and Pharmaceutical Bulletin **16**(4): 372-374.
- Shrivastava, S., T. Bera, et al. (2007). "Characterization of enhanced antibacterial effects of novel silver nanoparticles." Nanotechnology **18**(22): 225103.
- Shrivastava, S., T. Bera, et al. (2009). "Characterization of Antiplatelet Properties of Silver Nanoparticles." ACS Nano **3**(6): 1357-1364.
- Silver, S. (2003). "Bacterial Silver Resistance: Molecular Biology and Uses and Misuses of Silver Compounds." FEMS Microbiology Reviews **27**(2-3): 341-353.
- Silver, S., L. Phung, et al. (2006). "Silver as biocides in burn and wound dressings and bacterial resistance to silver compounds." Journal of Industrial Microbiology and Biotechnology **33**(7): 627-634.
- Skebo, J. E. (2007). "Assessment of Metal Nanoparticle Agglomeration, Uptake, and Interaction Using High-Illuminating System." International Journal of Toxicology **26**(2): 135-141.
- Sondi, I. and B. Salopek-Sondi (2004). "Silver nanoparticles as antimicrobial agent: a case study on *E. coli* as a model for Gram-negative bacteria." Journal of Colloid And Interface Science **275**(1): 177-182.
- Steffensen, K. L., O. J. Mesna, et al. (1994). "Cytotoxicity and accumulation of Hg, Ag, Cd, Cu, Pb and Zn in human peripheral T and B lymphocytes and monocytes *in vitro*." General Pharmacology **25**(8): 1621-1633.
- Sudmann, E., H. Vik, et al. (1994). "Systemic and local silver accumulation after total hip replacement using silver-impregnated bone cement." Medical Progress through Technology **20**: 179-184.
- Sugawara, N. and C. Sugawara (1984). "Comparative study of effect of acute administration of cadmium and silver on ceruloplasmin and metallothionein: Involvement of disposition of copper, iron, and zinc." Environmental Research **35**(2): 507-515.
- Sung, J. H., J. H. Ji, et al. (2009). "Subchronic inhalation toxicity of silver nanoparticles." Toxicological Sciences **108**(2): 452-461.
- Takenaka, S., E. Karg, et al. (2001). "Pulmonary and systemic distribution of inhaled ultrafine silver particles in rats." Environmental Health Perspectives **109**(Suppl 4): 547-551.
- Tomi, N. S., B. Kranke, et al. (2004). "A silver man." The Lancet **363**: 532.
- Tsai, S.-J., E. Ada, et al. (2009). "Airborne nanoparticle exposures associated with the manual handling of nanoalumina and nanosilver in fume hoods." Journal of Nanoparticle Research **11**: 147-161.
- Vallery-Radot and Pasteur (1936). Compt. Rend. Soc. de Biology **121**: 634.

- Van Vleet, J. F. (1976). "Induction of lesions of selenium-Vitamin E deficiency in pigs fed silver." American Journal of Veterinary Research **37**(12): 1415-1420.
- Vijan, S. R., M. A. Keating, et al. (1988). "Urethral stenosis after silver nitrate instillation in the treatment of essential hematuria." Journal of Urology **139**: 1015-1016.
- Vik, H., K. J. Andersen, et al. (1985). "Neuropathy caused by silver absorption from arthroplasty cement." The Lancet **April 13**: 872.
- Westhofen, M. and H. Schafer (1986). "Generalized argyrosis in man: neurotological, ultrastructural and X-ray microanalytical findings." Archives of Otorhinolaryngology **243**: 260-264.
- White, J. M., A. M. Powell, et al. (2003). "Severe generalized argyria secondary to ingestion of colloidal silver protein." Clinical Dermatology **28**: 254-256.
- Wijnhoven, S. W. P., W. Peijnenburg, J. G. M., et al. (2009). "Nano-silver--A review of available data and knowledge gaps in human and environmental risk assessment." Nanotoxicology **3**(2): 109-138.
- Wise, J. P., B. C. Goodale, et al. (2010). "Silver nanospheres are cytotoxic and genotoxic to fish cells." Aquatic Toxicology **97**(1): 34-41.
- Wu, Y., Q. Zhou, et al. (2010). "Effects of silver nanoparticles on the development and histopathology biomarkers of Japanese medaka (*Oryzias latipes*) using the partial-life test." Aquatic Toxicology **100**(2): 160-167.
- Zapata-Sirvent, R. and J. F. Hansbrough (1993). "Cytotoxicity to human leukocytes by topical antimicrobial agents used for burn care." Journal of Burn Care & Rehabilitation (14): 132-140.