MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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July 9, 1997

TO: File for Silver (CAS # 7440-22--4)

FROM: Dan O'Brien, Toxics Unit, Air Quality Division

SUBJECT: Initial Threshold Screening Level (ITSL) for Silver

The initial threshold screening level for silver metal dust and fume and soluble silver compounds (as silver) is 0.1 µg/m^3 based on an 8 hour averaging time.

The following references or databases were searched to identify data to determine the ITSL: AQD chemical files, IRIS, HEAST, ACGIH TLV Booklet, NIOSH Pocket Guide to Chemical Hazards, RTECS, NTP Management Status Report, EPB Library, IARC Monographs, CAS On-line and NLM/Toxline (1967 - November 13, 1996), CESARS, Patty's Industrial Hygiene and Toxicology, Merck Index and Condensed Chemical Dictionary.

Silver (Ag) is a hard, brilliant white, lustrous, ductile and malleable metal (ACGIH, 1992). It has found use in a number of applications, including manufacture of coinage, photographic chemicals, solder, mirrors, ethylene, electrical equipment (printed circuits, conductors, contacts and magnet windings), jewelry, cutlery, batteries, dental amalgam, and medical, dental, and scientific equipment (Beliles, 1994; ACGIH, 1992; Merck, 1983; Hawley, 1981). Other uses include in brazing alloys, bearing metal, electroplating, water distillation, as a sterilant, and as a lining in chemical reaction vessels.

With respect to acute toxicity, Beliles (1994) has stated that acute human toxicity from Ag is unknown, but some Ag compounds (Ag oxide, Ag nitrate) are irritating, and exposure is associated with nosebleeds and abdominal cramps. Acute irritation of the respiratory tract occurs at concentrations considerably higher than those that produce mucous membrane and ocular argyria (discussed below). RTECS (1996) lists acute oral LD_{50}s for Ag from the Russian literature in mice and guinea pigs of >10 g/kg and >5 g/kg, respectively. In comparison to Ag metal, ACGIH (1992) cites a study by Walker (1971) that records wide disparity in the acute oral toxicity of Ag compounds. For example, the LD_{Lo} for Ag_20 is recorded as being nearly 3 g/kg in the rat, while Ag nitrate, the most toxic of the five Ag compounds tested, had an oral LD_{50} of 50 mg/kg in the mouse.

Argyria (sometimes referred to as argyrosis, especially when affecting the eyes), a medically benign blue-gray discoloration of the skin and eyes, is the main result of chronic inhalation exposure to Ag (Beliles, 1994; ACGIH, 1992; ATSDR, 1990). It is caused by accumulation of Ag bound to sulfhydryl proteins, and also from Ag- induced production of melanin (IRIS, 1992). It is considered by EPA to be the critical effect for humans ingesting Ag as well. The eyes, skin, gums and pharynx are commonly affected, with gingival lines considered to be a characteristic first sign. Skin deposition occurs in the dermal layer, and thus is permanent. Ocular pigmentation has reportedly been seen more often than skin pigmentation (Beliles, 1994), with conjunctival pigmentation occurring first, with some localization to the inner canthus (NIOSH/OSHA, 1981). Although Ag has been shown to be uniformly deposited in exposed and unexposed areas of skin, the increased pigmentation becomes more pronounced in areas exposed to sunlight due to photoactivated reduction of the metal (IRIS, 1992). No pathologic changes or inflammatory reactions have been shown to result from Ag deposition. Much of what is known about argyria derives from the widespread therapeutic use of Ag arsphenamine as an antimicrobial treatment for syphilis in the late nineteenth and early twentieth centuries. Reviews have been published by Greene and Su (1987), Hill and Pillsbury (1939), and Gaul and Staud (1935). Other data (including essentially all of the human inhalation data) have followed from occupational studies. In addition to the argyria that has been reported in silver soldering workers and workers in the photographic, plating and precious metals industries, Rosenman et al (1987) noted a possible nephrotoxic effect. In a cross-sectional study of 27 precious metals workers, these authors found significantly increased urinary activity of N-acetyl-β-D-glucosaminidase in four workers (15%). Increased activity was correlated with age and blood Ag concentration. Moreover, the estimated creatinine clearance was lower in the Ag-exposed workers than in controls. However, a slight elevation of urinary cadmium (Cd) concentrations suggested that the abnormalities may have been due to the confounding effects of Cd. Thirty percent (8) workers complained of respiratory symptoms and nosebleeds. Argyrosis of the corneas was seen among the long term workers, and was associated with complaints of reduced night vision. A slight decline in visual adaptation to darkness was also reported in 4 plating workers (Osinska et al., 1982). Yet Osinska and others (Pifer et al., 1989) have also failed to find any substantial adverse health effects in workers with clinical evidence of argyria. These findings were similar to those reported in two workers employed in reclamation of Ag from used radiographic and photographic film (Williams and Gardner, 1995). They noted no clinical signs or symptoms in either worker, despite the fact that blood Ag concentrations exceeded those that have been associated with argyric neuropathy. Blood Ag concentrations were 49 µg/L in a 42 year old male exposed for 2 years, and 74 µg/L in a 51 year old male exposed for 7 years. Only the latter displayed clinical argyrosis. At least one reference unavailable for our review (Rose, 1992) notes an association of Ag oxides with metal fume fever. Argyria of the respiratory tract has been described in two workers involved in the manufacture of silver nitrate; their only symptom was mild, chronic bronchitis. Biopsy of the nasal mucous membrane showed silver deposition in the subepithelial area (NIOSH/OSHA, 1981).

While EPA has not established an inhalation Reference Concentration (RfC), it has developed an oral Reference Dose (RfD). Interestingly, this RfD is based on case series data from humans that developed argyria while being treated with intravenous injections of Ag arsphenamine for syphilis. The key study was that of Gaul and Staud (1935). The i.v. portion of the study described 10 male (23-64 years old) and

2 female (23 and 49 years old) patients who were administered 31-100 i.v. injections over a 2 to 9.75 year period. The cumulative dose at which each developed clinical argyria was somewhat variable, ranging from 4-20 grams. The authors concluded that argyria may become clinically apparent after a total accumulated dose of approximately 8 grams of Ag. This same cumulative dose figure was arrived at by Hill and Pillsbury (1939), although it is not known whether they based this conclusion on independent work or merely were citing the earlier work of Gaul and Staud. With an eye towards assessing risk to sensitive groups however, EPA assumed that the body accumulates silver throughout life, and that consequently, "it is theoretically possible for amounts less than this (for example, 4 g silver arsphenamine) to result in argyria" (IRIS, 1992). Thus, EPA concluded "the lowest i.v dose that resulted in argyria in one patient, I g metallic silver (4 g silver arsphenamine X 0.23, the fraction of silver in silver arsphenamine) is considered to be a minimal effect level for this study". This dose was adjusted to an oral basis by dividing this minimal effect level by 0.04 [assuming an oral retention factor of 4.4% for a 70 kg human, based on the metabolic work of Furchner et al. (1968)[1]]. The resulting 25 g whole body oral dose which constituted the human Lowest Observed Adverse Effect Level (LOAEL) was then divided by 70 kg (default human adult body weight) and 25,500 days in an assumed seventy year lifetime to yield an $LOAEL_{(ADJ)}$ of 0.014 mg/kg-day. That figure was further divided by an uncertainty factor (UF) of 3 to yield the RfD of 0.005 mg/kg-day, or 5 µg/kg-day. The UF of 3 was used to account for a minimal effect (argyria is essentially a cosmetic effect only) that was exhibited in a subpopulation already demonstrated to be more sensitive to the effects of Ag than the rest of the study population. Moreover, the studied population was already suffering from chronic disease (syphilis), and thus may have been more sensitive to intoxication than the general population. EPA assigned low to medium confidence to the RfD.

ATSDR has published a Toxicological Profile for Ag (ATSDR, 1990) which provides extensive documentation of the literature current to that date. It does not, however, include calculation of Minimal Risk Levels. Literature described in detail in the Profile include information on toxicokinetics and reproductive/developmental toxic endpoints. With respect to the former, limited data from a single human accidentally exposed to radioactive Ag (Newton and Holmes, 1966), and an inhalation study in dogs (Phalen and Morrow, 1973) are available. Newton and Holmes used whole-body gamma-ray spectrometry to measure absorption, distribution and elimination of ^{110m}Ag in a worker exposed by inhalation during a nuclear reactor mishap. They estimated that the greatest amount of absorbed Ag was distributed to the liver, with 25% of the detectable concentration partitioned there between days 2 and 6 post-exposure. ^{110m}Ag was rapidly cleared from the lungs via the mucociliary escalator with subsequent ingestion and elimination in the feces. Lung clearance was biexponential, with biological half-lives of 1 and 52 days. Radioactive silver was detected in feces for "up to" 300 days after exposure. In contrast, Phalen and Morrow found the primary route of lung clearance in laboratory animals to be

[1] Furchner and coworkers (1968) studied the absorption and retention of ingested silver in mice, rats, monkeys and dogs. Little Ag was absorbed from the gastrointestinal tract of any of the species, with cumulative excretion ranging from 90-99% in all species by the second day. The dog retained the most Ag, and so the dog data was used in a retention equation which was integrated from zero to infinity according to a triphasic elimination pattern in order to estimate how much of the Ag ingested by a 70 kg human would be retained.

through dissolution of the silver and transport through the blood. The largest site of deposition was again the liver, but mucociliary clearance was determined to have played a little role. Clearance from the lung was triexponential in dogs, with biological half lives of 1.7, 8.4 and 40 days, accounting for 59, 39 and 2% of the radioactivity excreted, respectively, in the feces. Excluding the silver deposited in the lung, 77% of the body burden of Ag was found in the liver. Excretion in both man and the animal species studied is primarily biliary, with a small amount excreted in the urine (ATSDR, 1990).

As for reproductive/developmental endpoints, no human data are available, but ATSDR (1990) notes that "the existing [animal] evidence does not point to a strong effect of silver on reproduction". However, no multigeneration reproductive studies apparently exist which might confirm this definitively. Ag is known to pass the placenta from mother to fetus, but available evidence is insufficient to judge the potential for developmental toxicity in humans.

The only references to the carcinogenicity of Ag discovered in our searches were abstracted from summary references (RTECS, 1996; CESARS, 1996; ACGIH, 1992). RTECS cited two studies (Oppenheimer et al, 1956) and another from a German journal dated 1955 in which Ag implants were used to gauge tumorigenicity. ACGIH notes that these and studies where colloidal Ag was injected have variably resulted in local development of fibrosarcomas (Furst and Schlauder, 1977; Schmahl and Steinhoff, 1960). In any case, tumors induced by these routes of exposure are of limited relevance to assessment of risks from inhaled Ag. CESARS (1996) has summarized these findings, noting that "it is generally accepted that the tumors which developed were the result of a solid state effect and silver is not a carcinogen". Thus, there appears to be no evidence of carcinogenicity as a critical endpoint with respect to human health risks from Ag exposure. Available mutagenicity data, though based on a small number of studies in limited test systems, are generally negative (CESARS, 1996).

The American Conference of Governmental Industrial Hygienists (ACGIH) has set a time-weighted average (TWA) Threshold Limit Value (TLV) for silver metal dust and fume of 0.1 mg/m^3, while the TLV for soluble Ag compounds (as Ag) is 0.01 mg/m^3. In contrast, the National Institute for Occupational Safety and Health (NIOSH) Recommended Exposure Level (REL) encompasses both Ag metal dust and soluble compounds as Ag, and is set at the same concentration as the TLV for soluble silver compounds (NIOSH, 1994; ACGIH, 1992)[2]. ACGIH (1992) has noted that "the concentration of silver in air that will result in generalized argyria is not known with certainty", but they appear to base their TLV primarily on Stokinger (1981). Stokinger cites unpublished personal communications with Eastman Kodak Company regarding their historical experience with argyria observed in their workers. Prior to 1940 when "atmospheric levels were of the order of 1 mg/m^3", cases of generalized argyria were observed; at "levels estimated to be of the order of 0.1 mg/m^3...some staining of the mucous membranes of the nose and throat and some eye discoloration" were noted, characteristic pigmentary changes which precede generalized argyria. This author reported no new cases of argyria or other adverse effects since that time in periodically monitored personnel. Silver concentrations in "high exposure areas" in this plant during the period during which no cases were noted averaged about 40 to 60 µg/m^3 with values as high as about 150 µg/m^3. ACGIH goes on to calculate that a 0.1 mg/m^3 concentration would result in a total

[2] One of the interim ITSLs set for Ag in January of 1993 was based on this REL; the other was based upon the RfD.

body deposition of no more than 1.5 g in 25 years[3]. This total body burden of Ag would be somewhat higher than the 1 g burden considered the minimal effect level for argyria by EPA in calculation of the RfD, though much lower than the 8 g figure which Hill and Pillsbury (1939) concluded would result in clinical argyria. NIOSH/OSHA (1981) has determined that "a total body burden from 1 to 5 g of silver will lead to generalized argyria". NIOSH (1994) provides little documentation for their REL, noting only the symptoms of argyria (blue-gray eyes, nasal septum, throat and skin), irritation and ulceration of the skin, and gastrointestinal disturbances as a basis. The latter two symptoms presumably apply to the nitrate of Ag, which is strongly corrosive, capable of causing burns on skin contact, and abdominal pain and gastroenteritis on ingestion (NIOSH/OSHA, 1981). Both NIOSH and ACGIH point out that dermal exposure to Ag can induce allergic contact dermatitis.

Derivation of the ITSL: In choosing data for screening level development, preference is generally given to human epidemiologic data or chronic laboratory animal studies which can be used to derive a Reference Concentration (RfC). Such data for Ag were not found in our searches. When adequate data for RfC calculation are not available, next preference is given to oral data for calculation of a Reference Dose (RfD) if available data do not indicate that extrapolation from the oral to the inhalation route of exposure is inappropriate. A potential disadvantage of using the RfD for Ag as basis for the ITSL lies in the fact that the RfD itself is based not on oral data, but on intravenous exposures extrapolated to the oral route. Use of the RfD would necessitate a second cross-route extrapolation (from the oral route to the inhalation route), and it seems likely that this would introduce more uncertainty into the screening level development process than is necessary or desirable. Moreover, there is arguably sufficient evidence to suggest that extrapolation from the RfD to an inhalation ITSL may be inappropriate. First, the prominence of the liver as a deposition site for absorbed Ag noted in the available kinetic studies suggests that a first-pass effect may occur following oral exposure. Second, contrasting results recorded in the human (Newton and Holmes, 1966) and dog (Phalen and Morrow, 1973) kinetic studies regarding the mechanism of systemic absorption following inhalation (mucociliary clearance vs. dissolution in the lung with blood transport, respectively), suggest that substantial uncertainty remains with respect to the toxicokinetics of inhaled Ag. Third, the disparity in the retention rates assumed in calculation of the RfD versus the TLV[3], suggests that a substantial difference may exist in the amount of Ag retained in the body after ingestion, as compared to the amount retained after inhalation.

The next most appropriate alternative is an ITSL based upon an OEL. Given the unavailability of other inhalation data of sufficient quality for derivation of an RfC, and the possible inappropriateness of the cross-route extrapolations necessary to use the RfD, an OEL is used here for the calculation of an ITSL for Ag. Essentially all of the available data regarding human inhalation exposures to Ag are derived from the occupational literature. Per rule 232(1) (c), the OEL-based ITSL is to be derived from the lowest value of either the REL or the TLV, which in this case is the REL.

[3] Assuming 25% retention upon inhalation and a daily (workday) respiratory volume of 10 m3. Note that this assumed that retention via the inhalation route is markedly higher than the 4.4% retention assumed by EPA following oral exposure. Unfortunately, ACGIH does not elaborate on why a 25% retention rate was assumed, or whether this figure was based on data or simply a conservative estimate.

Per Rule 232(1) (c), part 55, of Act 451:

ITSL = OEL x 1/100 = 0.01 mg/m^3 x 1/100 = 0.0001 mg/m^3 x 1000 µg/1mg= 0.1 $µg/m^3$

where the factor of 1/100 is a safety factor to account for: 1) differences in susceptibility between the healthy, adult worker population as compared to the general population which may include individuals or subpopulations more sensitive to the effects of exposure to Ag and 2) the difference in exposure duration for the worker population as opposed to the general population. The factor is derived as follows:

Safety factor = 40 hours /168 hours x 30 years/70 years x 1/10 =1/100

The first term adjusts for the difference between a 40 hour work week and the total hours in a week; the second factor adjusts for the difference between an assumed working life of 30 years and an assumed total lifespan of 70 years; and the third factor is a standard tenfold uncertainty factor to extrapolate from the healthy worker to sensitive individuals in the general population.

It should be noted that this ITSL applies to Ag metal dust and fume and soluble Ag compounds taken as a group. However, screening levels for soluble Ag compounds should ideally be derived on a case by case basis as chemical-specific data allow. Based solely on the OELs, there is a suggestion that soluble Ag compounds are considered to be at least an order of magnitude more toxic than Ag metal dust and fume.

Consistent with 232 (2) (a), since the OEL used here is based on a time-weighted average, an **8 hour averaging time** applies.

REFERENCES

ACGIH (1992). Silver and Compounds. In: Documentation of Threshold Limit Values Biological Exposure Indices, American Conference of Governmental Industrial Hygienists, Cincinnati, pp. 1396-1400.

ATSDR (1990). Toxicological Profile for Silver. Prepared by Clement International Corporation for the Agency for Toxic Substances and Disease Registry, Public Health Service, U.S. Department of Health and Human Services, 145 pp.

Beliles, R.P. (1994). 28. Silver (Ag). In: Patty's Industrial Hygiene and Toxicology, 4th Ed. (Clayton, G.D and Clayton F.E., Eds.), Volume II, Part C, Chapter Twenty-Seven: The Metals. John Wiley and Sons, Inc., New York, pp. 2210-2216.

CESARS (1996). #683: Silver (7440-22-4). Chemical Evaluation Search and Retrieval System, Ontario Ministry of the Environment and Michigan Department of Natural Resources.

Furchner, J.E., Richmond, C.R. and Drake, G.A. (1968). Comparative metabolism of radionuclides in mammals - IV. Retention of silver -110m in the mouse, rat, monkey and dog. *Health Phys* 15:505-514.

Furst, A. and Schlauder, M.C. (1977). Inactivity of two noble metals as carcinogens. *J Environ Pathol Toxicol* 1:51-57 [cited in ACGIH, 1992].

Gaul, L.E. and Staud, A.H. (1935). Clinical spectroscopy. Seventy cases of generalized argyrosis following organic and colloidal silver medication including a biospectrometric analysis of ten cases. *J Am Med Assoc* **104**(16):1387-1390.

Greene, R.M. and Su, W.P.D. (1987). Argyria. *Am Fam Phys* 36:151-154.

Hawley, G.G. (1981). The Condensed Chemical Dictionary. Tenth Ed. Van Nostrand Reinhold Company, New York, p. 923.

Hill, W.R. and Pillsbury, D.M. (1939). Argyria. The Pharmacology of Silver. Williams and Wilkins, Baltimore [cited in IRIS, 1992].

IRIS (1992) . Silver (7440-22-4). Integrated Risk Information System, U.S. Environmental Protection Agency.

Merck (1983). Merck Index: An Encyclopedia of Chemicals, Drugs and Biologicals, (Windholz, M., Ed.) Tenth Ed. Merck and Company, Rahway, N.J., p. 1221.

Newton, D. and Holmes, A. (1966). A case of accidental inhalation of zinc-65 and silver-110m. *Radiat Res* **29**:403-412.

NIOSH (1994). NIOSH Pocket Guide to Chemical Hazards. National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Public Health Service, U.S. Department of Health and Human Services. DHHS (NIOSH) publication #94-116, p. 280.

NIOSH/OSHA (1981). Occupational health guideline for silver metal and soluble silver compounds. NIOSH/OSHA Occupational Health Guidelines for Chemical Hazards (Mackison, F.W., Stricoff, R.S. and Partridge, L.J., Jr., Eds.). National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Public Health Service, U.S. Department of Health and Human Services, and Occupational Safety and Health Administration, U.S. Department of Labor. DHHS (NIOSH) publication #81-123, 5 pp.

Oppenheimer, B.S., Oppenheimer, E.T. and Danishefsky, I., et al. (1956). Carcinogenic effect of metals in rodents. *Cancer Res* 16:439-441 [cited in RTECS, 1996 and ACGIH, 1992].

Osinska, J. et al. (1982). *Med Pr* **33**:361 [cited in Beliles, 1994].

Phalen, R.F. and Morrow, P.E. (1973). Experimental inhalation of metallic silver. *Health Phys* **24**:509-518.

Pifer, J.W., et al. (1989). *Scand J Work Environ Health* **15**:210 [cited in Beliles, 1994].

Rose, C.S. (1992). Inhalation fevers. In: Environmental and Occupational Medicine, Second Ed. (Rom, W.N., Ed.). Little, Brown, and Co., Boston, pp. 373-380.

Rosenman, K., et al. (1987). *Br J Ind Med* **44**:267 [cited in Beliles, 1994].

RTECS (1996). Silver (7440-22--4). In: Registry of Toxic Effects and Chemical Substances Database. National Institute for Occupational Safety and Health, Public Health Service, Centers for Disease Control, U.S. Department of Health and Human Services, and Canadian Centre for Occupational Safety and Health.

Schmahl, D. and Steinhoff, D. (1960). Experimental carcinogenesis in rats with colloidal silver and gold solutions. *Z Krebsforsc* **63**:586-591 [cited in ACGIH, 1992].

Stokinger, H.E. (1981). 29. Silver, Ag. In: Patty's Industrial Hygiene and Toxicology, 3rd Ed. (Clayton, G.D and Clayton F.E., Eds.), Volume 2A, Chapter Twenty-Nine: The Metals. John Wiley and Sons, Inc., New York, pp. 1881-1893.

Walker, F. (1971). Experimental argyria. A model for basement membrane studies. *Br J Exp Pathol* **52**:589-593 [cited in ACGIH, 1992].

Williams, N. and Gardner, I. (1995). Absence of symptoms in silver refiners with raised blood silver levels. *Occup Med* **45**(4): 205-208.

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