2. HEALTH EFFECTS

2.1 INTRODUCTION

This chapter contains descriptions and evaluations of studies and interpretation of data on the health effects associated with exposure to silver. Its purpose is to present levels of significant exposure for silver based on toxicological studies, epidemiological investigations, and environmental exposure data. This information is presented to provide public health officials, physicians, toxicologists, and other interested individuals and groups with (1) an overall perspective of the toxicology of silver and (2) a depiction of significant exposure levels associated with various adverse health effects.

Silver occurs naturally in several oxidation states. The most common are elemental silver (0 oxidation state) and the monovalent silver ion (+1 oxidation state). Most of the toxicological studies of silver have investigated these chemical forms of the element. Other possible oxidation states of silver are +2 and +3, however, no toxicological studies were located that researched the health effects of silver compounds with these oxidation states. Most occupational exposures to silver occur through inhalation of silver-containing dusts or dermal exposure to photographic compounds. Published studies on human inhalation of silver are based predominantly on exposure to elemental silver, silver nitrate, and silver oxide. Human oral data come from information on medicines containing silver, such as silver acetate-containing antismoking lozenges, breath mints coated with silver, and silver nitrate solutions for treating gum disease. Animal studies usually are based on exposure to silver nitrate and silver chloride in drinking water. Humans may be dermally exposed to silver through the use of silver-containing processing solutions for radiographic and photographic materials, dental amalgams, and medicines (e.g., silver sulphadiazine cream and solutions for treating burns).

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals address the needs of persons living or working near hazardous waste sites, the data in this section are organized first by route of exposure -- inhalation, oral, and dermal -- and then by health effect -- death, systemic, immunological, neurological, developmental, reproductive, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods -- acute, intermediate, and chronic. Levels of significant exposure for each exposure route and duration (for which data exist) are presented in tables and illustrated in figures. The

points in the figures showing no-observed-adverse-effect levels (NOAELS) or lowest-observed-adverse-effect levels (LOAELS) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear, determine whether or not the intensity of the effects varies with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown on the tables and graphs may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons or with the identification of persons with the potential to develop such disease may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers concerned with response actions at Superfund sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAEL) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels, MRLs) are of interest to health professionals and citizens alike.

Estimates of exposure posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer end point for each exposure duration. MRLs include adjustments to reflect human variability and, where appropriate, the uncertainty of extrapolating from laboratory animal data to humans. Although methods have been established to derive these levels (Barnes et al. 1987; EPA 1989a), uncertainties are associated with the techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of these procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

2.2.1 Inhalation Exposure

2.2.1.1 Death

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

2.2.1.2 Systemic Effects

No studies were located regarding cardiovascular or musculoskeletal effects in humans or animals after inhalation exposure to silver or silver compounds.

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Respiratory Effects. Respiratory effects have been observed infrequently in humans following inhalation of silver compounds. In one case report of a worker who had become ill 14 hours after he had been working with molten silver ingots, symptoms were limited primarily to the respiratory system (Forycki et al. 1983). Unfortunately, the concentration and chemical composition of the silver in the work room air were not known, and the history of exposure to silver prior to this incident was not reported. The initial symptoms seen in this patient included audible crackles during breathing, rapid pulse, low oxygen content of capillary blood, and scattered thickening of the lungs observed in chest radiograms. The patient's symptoms progressed to acute respiratory failure, from which the patient eventually recovered fully.

Occupational exposure to silver dusts can also lead to respiratory irritation (Rosenman et al. 1979, 1987). One occupational study describes a group of 30 employees of a manufacturing facility involved in the production of silver nitrate and silver oxide (Rosenman et al. 1979). The average air level of these silver compounds over the duration of the workers' exposure was not estimated. However, personal air monitoring conducted 4 months previous to the study determined an 8 hour time-weighted average (TWA) concentration range of 0.039 to 0.378 mg silver/m^3. Duration of employment ranged from less than one, to greater than ten years. Twenty-five of the 30 workers complained of upper respiratory irritation (sneezing, stuffiness, and running nose or sore throat) at some time during their employment, with 20 out of 30 complaining of cough, wheezing, or chest tightness. Chest radiograms and results of clinical examination of respiratory function were predominantly normal, with no demonstrated relationships between abnormalities and duration of employment. Similar complaints were recorded for workers involved in the manufacture of silver metal powders, although the workers were concurrently exposed to acids, hydroquinone, formaldehyde, caustics, solvents, and cadmium (Rosenman et al. 1987).

Acute (2-8 hours) inhalation of an aerosol containing colloidal silver by rabbits (whole body exposure, concentrations not given) has been reported to lead to ultrastructural damage and disruption of cells of the tracheal epithelium (Konradova 1968).

Gastrointestinal Effects. Abdominal pain has also been reported by workers exposed to silver nitrate and oxide in the workplace (Rosenman et al. 1979). The pain was described as "burning in quality and relieved by antacids" and was reported in 10 out of 30 workers examined. Exposure levels were estimated to be between 0.039 and 0.378 mg silver/m^3. No information on chemical form or particle size was provided. Duration of employment ranged from less than one, to greater than ten years. This symptom correlated significantly with blood silver levels, indicating that those workers exposed to higher levels of airborne silver nitrate and/or oxide are more likely to suffer gastrointestinal pain.

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No studies were located regarding gastrointestinal effects in animals following inhalation exposure to silver or silver compounds.

Hematological Effects. Blood counts were reported to be normal in all individuals observed in the occupational study of silver-exposed workers conducted by Rosenman et al (1979) with the exception of one individual with an elevated hemoglobin level. In a study by Pifer et al. (1989), silver reclamation workers chronically exposed to insoluble silver compounds (e.g., the silver halides) exhibited a marginal decrease in red blood cell count, as well as an increase in mean corpuscular volume. However, the toxicological significance of these findings is unclear.

No studies were located regarding hematological effects in animals following inhalation exposure to silver or silver compounds. Despite the lack of supportive animal data, occupational exposure findings suggest that hematological effects are not a sensitive indicator of silver toxicity.

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

No studies were located regarding hepatic effects in animals following inhalation exposure to silver or silver compounds.

Renal Effects. Occupational exposure to silver metal dust has been associated with increased excretion of a particular renal enzyme (N-acetyl-β-D glucosaminidasej, and with decreased creatinine clearance (Rosenman et al. 1987). Both of these effects are diagnostic of marginally impaired renal function. However, the workers in this study were also exposed to cadmium, which was detected in the urine of 5 of the 27 workers studied. Cadmium is known to be nephrotoxic; differentiation of the effects of the two metals in the kidney is not possible with the data presented. Therefore, no conclusion can be drawn regarding renal effects of silver based on this study.

No studies in animals were located which support the observation of renal effects in the Rosenman et al (1987) study. Studies in animals have focused only on the deposition of silver in the kidney following oral exposure (Olcott 1947; 1948) and renal function tests were not conducted.

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

Granular deposits were observed in the conjunctiva and cornea of the eyes of 20 out of the 30 workers in the occupational study of Rosenman et al.

(1979), and subjective determination of the degree of silver deposition in the conjunctiva correlated with the duration of employment (see also Moss et al. 1979). Furthermore, the amount of deposition in the eyes was found to correlate significantly with reports of changes in skin color and decreased night vision. The complaint of decreased night vision was also recorded in a study of workers involved in the manufacture of metal silver powders (Rosenman et al. 1987).

An investigation of silver reclamation workers found that 21% and 25% exhibited conjunctival and cornea1 argyrosis (silver staining or deposition), respectively (Pifer et al. 1989). Moreover, 74% of the subjects exhibited some degree of internal nasal-septal pigmentation. However, no association was observed between silver deposition and ocular impairment.

In another report describing the same cohort of workers as studied by Rosenman et al. (1979), Moss et al. (1979) conducted electrophysiological and psychophysiological studies of the eyes of 7 of the 10 workers who had complained of decreased night vision. No functional deficits were found in the vision of these workers.

The relative contributions of dermal/ocular absorption, ingestion, and inhalation of silver compounds to the development of these ocular deposits and skin color changes are not known. However, granular deposits containing silver have been observed to-develop in various ocular tissues of animals following ingestion of silver compounds, and it is likely that systemic absorption following inhalation exposure also results in silver deposition (Matuk et al 1981; Olcott 1947; Rungby 1986). The possibility remains that the deposits were in some proportion caused by direct exposure of the eyes to airborne silver compounds.

No studies were located regarding dermal or ocular effects in animals following inhalation exposure to silver or silver compounds.

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

2.2.1.3 Immunological Effects

2.2.1.4 Neurological Effects

2.2.1.5 Developmental Effects

2.2.1.6 Reproductive Effects

2.2.1.7 Genotoxic Effects

2.2.1.8 Cancer

2.2.2 Oral Exposure

2.2.2.1 Death

No studies were located regarding death in humans following oral exposure to silver or silver compounds.

Death has been observed in rats following ingestion of colloidal silver and inorganic silver compounds. In each case the level of silver was very high. For example, death was reported in rats (number not specified) following acute oral ingestion of silver colloid (Dequidt et al. 1974). In another study, Walker (1971) reported deaths in 3 of 12 rats during a 2-week exposure to silver nitrate in drinking water. Cause of death was not reported in either of these studies. However, the rats in the Walker (1971) study were observed to decrease their water intake "precipitously" beginning on the 1st day of exposure, and survivors were generally described as "poorly groomed and listless" at the end of the exposure. No lethality occurred in a lower dose group.

Death was also reported in an unspecified number of rats receiving 222.2mg silver/kg/day as silver nitrate in drinking water over a longer duration (Matuk et al. 1981). The deaths began occurring approximately 23 weeks into 37-week experiment during which the exposed animals also showed a decreased weight gain compared to animals receiving only water. The highest NOAEL values and all reliable LOAEL values for death in each species and duration are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.2.2 Systemic Effects

No studies were located regarding respiratory, gastrointestinal, hematological, musculoskeletal, hepatic, or renal effects in humans or animals after oral exposure to silver or silver compounds.

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

One study reported enlargement of the left ventricle in rats following 9-29 months of oral exposure to silver nitrate or silver chloride in drinking water (Olcott 1950). Left ventricle size (expressed as a ratio of ventricle weight to body weight) increased with exposure,duration, and showed a tendency to increase with dose of silver. The authors suggest that the increase in ventricle size could be caused by hypertension, but no blood pressure measurements were performed. Gross and histopathological examination of the tissues revealed only a few scattered granular deposits in the heart. The effect on left ventricle size was seen at a dose of 88.9 mg silver/kg/day;

TABLE 2-1. Levels of Significant Exposure to Silver* - Oral

Figure Key	Species	Route	Exposure Frequency/ Duration	Effect	NOAEL (mg Ag/kg/day)	LOAEL (Effect) Less Serious (mg Ag/kg/day)	LOAEL (Effect) Serious (mg Ag/kg/day)	Reference
ACUTE EXPOSURE								
Death								
1	Rat	NS	4 d 1x/d				1680	Dequidt et al. 1974
2	Rat	(W)	2 wk 7d/wk		181.2		362.4[a] (3/12)	Walker 1971
INTERMEDIATE EXPOSURE								
Systemic								
3	Rat	(W)	37 wk 7d/wk	Other		222.2[b] (< weight gain)		Matuk et al. 1981
Neurological								
4	Mouse	(W)	125 d 7d/wk			18.1[c] (hypoactivity)		Rungby and Danscher 1984

*Presented as elemental silver.

[a]Converted to an equivalent concentration of 2,589 ppm in water for presentation in Table 1-4.
[b]Converted to an equivalent concentration of 1,587 ppm in water for presentation in Table 1-4.
[c]Converted to an equivalent concentration of 95 ppm in water for presentation in Table 1-4.

mg/kg/day = milligrams per kilogram per day; NS = not specified; d = day; (W) = drinking water; wk = week; x = time(s); < = decreased.

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FIGURE 2-1. Levels of Significant Exposure to Silver - Oral

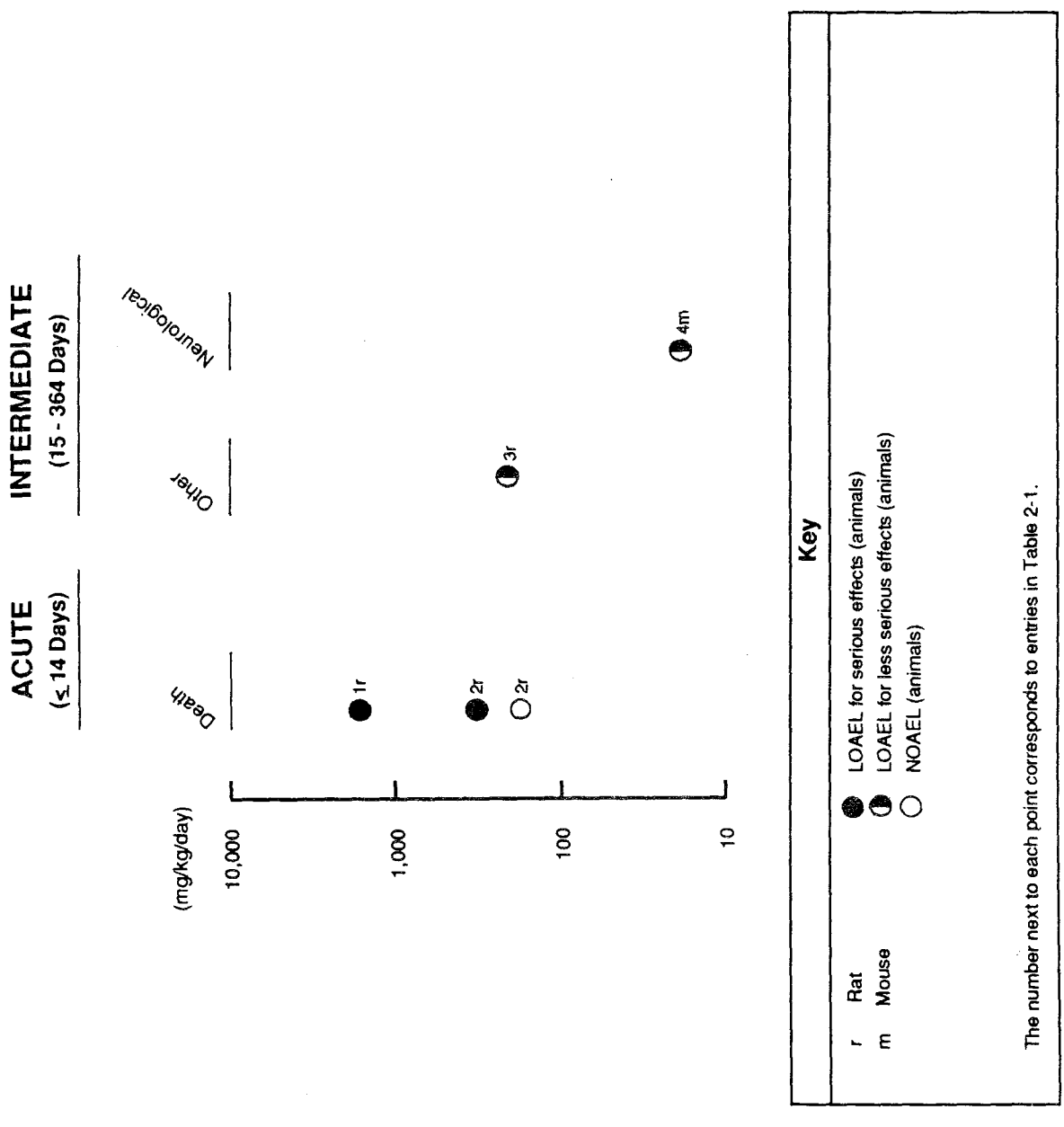

FIGURE 2-1. Levels of Significant Exposure to Silver - Oral

however, limitations of the study such as poor experimental design and inadequate reporting of methods preclude use of these data to predict equivalent levels of exposure in humans.

Dermal/Ocular Effects. Gray or blue-gray discoloration of the skin has been observed in individuals that have ingested both metallic silver and silver compounds in small doses over periods of months to years. Silver containing granules have been observed during histopathologic examination of the skin of these individuals. The condition is termed "argyria." Unfortunately, only rough estimates of the amount of silver ingested were located, and therefore precise levels of exposure resulting in discoloration cannot be established.

Case histories of argyria have been published concerning individuals who had ingested silver through excessive use of antismoking lozenges containing silver acetate, silver nitrate solutions for the treatment of gum disease, breath mints coated with metallic silver, and capsules containing silver nitrate for the relief of gastrointestinal "discomfort" (Aaseth et al. 1981; Blumberg and Carey 1934; East et al. 1980; MacIntyre et al 1978; Marshall and Schneider 1977; Shelton and Goulding 1979; Shimamoto and Shimamoto 1987). In general, quantitative data were nonexistent or unreliable and could not be used to establish LOAELs. The only common symptom among these cases was the resulting gray pigmentation of the skin of primarily sun-exposed regions. Examination of skin biopsies. from these individuals at the light microscopic level revealed granular deposits in the dermis. The granules were distributed throughout the dermis, but were particularly concentrated in basement membrane and elastic fibers surrounding sweat glands. The granules have been observed to contain silver (Bleehen et al. 1981; MacIntyre et al. 1978).

Ingestion of silver nitrate and silver chloride will also cause deposition of silver granules in the skin of animals (Olcott 1948; Walker 1971). However, skin discoloration in animals following exposure to these silver compounds has not been studied specifically, and the level of deposition that leads to skin discoloration in humans cannot be established based on existing animal data. Granules are also observed in the eyes of rats exposed to silver nitrate in drinking water at doses that cause general deposition in other tissues (Matuk et al. 1981; Olcott 1947; Rungby 1986). The number of deposits in the eyes is related to the degree of yellow-to-darkgray pigmentation observed at gross examination, which in turn is related to the duration of exposure.

Other Systemic Effects. Rats receiving 222.2 mg silver/kg/day in their drinking water lost weight over a 37 week exposure period. Weight loss first appeared about 23 weeks into the experiment, and the authors observed that several animals that lost weight rapidly died. Body weight in the surviving experimental animals was an average of 50% less than that of control rats

drinking only distilled water over the same exposure period (Matuk et al. 1981).

2.2.2.3 Immunological Effects

No studies were located regarding immunological effects in humans or animals following oral exposure to silver or silver compounds.

2.2.2.4 Neurological Effects

Several reports describe the deposition of what are assumed to be silvercontaining granules in tissues of the central nervous system. One report describes such granules in certain areas of the brain of an argyric woman at autopsy (Landas et al. 1985) who had used nose drops containing silver nitrate (concentration not specified) for an unspecified duration. The areas of the brain described as containing silver in the Landas et al (1985) study are known to have more direct exposure to blood-borne agents than other areas (e.g., the "circumventricular organslt, and the paraventricular and supraoptic nuclei of the hypothalamus). Unfortunately, the study examines only these specialized areas, and so does not provide complete information on the distribution of silver throughout the brain. There is no evidence that clearly relates the existence or deposition of these granules to a neurotoxic effect of silver exposure.

However, one study has found that 20 female mice exposed to silver nitrate in drinking water for 4 months, and observed to have such deposits in the central nervous system, were less active (hypoactive) than unexposed controls (Rungby and Danscher 1984). Activity was easured using a blind assay. The highest concentration of granular deposits occurred in certain areas involved in motor control (i.e., red nucleus, deep cerebellar nuclei, and motor nuclei of the brainstem), with lesser amounts observed in the basal ganglia, the anterior olfactory nucleus, and in the cortex in general. A specific relationship between the deposition of granules in these brain areas following silver ingestion and the decrease in gross activity has not been established. The highest NOAEL values and all reliable LOAEL values for neurological effects in each species and duration are recorded in Table 2-l and plotted in Figure 2-1.

2.2.2.5 Developmental Effects

No studies were located regarding developmental effects in humans or animals after oral exposure to silver or silver compounds.

2.2.2.6 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to silver or silver compounds.

No diminution of fertility was observed in male rats exposed,. for up to 2 years, to 88.9 mg silver/kg/day as silver nitrate or silver chloride in drinking water (Olcott 1948). Appearance of spermatozoa was normal, and no silver deposits were observed in the testes. Unfortunately, poor experimental design and reporting of methods preclude use of these data in determining a no effect level for male reproductive effects.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after oral exposure to silver or silver compounds.

2.2.2.8 Cancer

No studies were located regarding cancer in humans or animals after oral exposure to silver or silver compounds.

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding death in humans following dermal exposure to silver or silver compounds.

Mortality following dermal application of silver nitrate has been investigated in guinea pigs (Wahlberg 1965). The investigators applied 2.0 mL of a 0.239 molar solution of silver nitrate, in water by skin depot to 3.1 cm^2 of skin for 8 weeks. No deaths were recorded; however, during the exposure period the guinea pigs ceased to gain weight. In concurrent investigations of equimolar amounts of other metal salts using the same methods, mercuric chloride and cobalt chloride caused the death of more than half of the test animals.

The NOAEL value for death is recorded in Table 2-2.

2.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, or ocular effects in humans or animals after dermal exposure to silver or silver compounds.

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

TABLE 2-2. Levels of Significant Exposure to Silver* - Dermal

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (mg Ag/kg/day)	LOAEL (Effect) Less Serious (mg Ag/kg/day)	LOAEL (Effect) Serious (mg Ag/kg/day)	Reference
INTERMEDIATE EXPOSURE							
Death							
1	Gn pig	8 wk 7d/wk (skin depot)		137.13			Wahlberg 1965
Systemic							
2	Gn pig	8 wk 7d/wk (skin depot)	Other		137.13 (< weight gain)		Wahlberg 1965

*Presented as elemental silver.

mg/kg/day = milligrams per kilogram per day; Gn pig = guinea pig; wk = week; d = day; < = decreased.

information (Buckley 1963; McMahon and Bergfeld 1983). Moreover, adverse effects such as argyria have not been associated with the use of silver sulphadiazine as a bactericidal agent (Fox et al. 1969). No studies were located regarding dermal effects in animals after dermal exposure to silver or silver compounds.

Other Systemic Effects. Decreased body weight gain was observed in guinea pigs following application of 81 mg silver nitrate (2 mL of a 0.239 M solution) to 3.1 cm^2 of skin. At the end of 8 weeks, the silver nitrate-exposed guinea pigs weighed approximately 10-20% less than unexposed controls and controls exposed to distilled water (Wahlberg 1965).

2.2.3.3 Immunological Effects

Medical case histories describe mild allergic responses attributed to repeated dermal contact with silver and silver compounds (Catsakis and Sulica 1978; Hey1 1979; Marks 1966). Sensitization occurred in response to contact with powdered silver cyanide, radiographic processing solutions, and apparently to silver in dental amalgam. The duration of exposure ranged from 6 months in a worker exposed to silver cyanide, 10 years for a woman employed as a radiograph processor, to 20 years for a woman whose allergy had apparently been caused by dental fillings. The concentration of silver that caused these allergic responses is not known. No studies were located' regarding immunological effects in animals after dermal exposure to silver or silver compounds.

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

2.2.3.4 Neurological Effects

2.2.3.5 Developmental Effects

2.2.3.6 Reproductive Effects

2.2.3.7 Genotoxic Effects

2.2.3.8 Cancer

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

Studies in humans regarding the absorption of silver following inhalation exposure are limited to occupational studies and a case study. It is assumed

that the predominant routes of exposure to silver in the workplace are inhalation and dermal, with the dermal route being more important when prolonged contact with silver in solution occurs (as in photographic processing). Given this assumption, existing studies suggest that silver and silver compounds can be absorbed when inhaled, although the degree of absorption, both absolute and relative to the degree of dermal absorption, is not known.

A case study involving an accidental exposure of one worker to radiolabeled silver metal during a nuclear reactor mishap supports the assumption that absorption of silver metal dust can occur following inhalation exposure (Newton and Holmes 1966). Radioactive silver was measured using whole-body gamma-ray spectrometry beginning two days after a one-time inhalation exposure and continued for up to 200 days. Localization of silver in the liver, and detection in feces indicated that passage through the lungs had occurred. Unfortunately this study did not measure exposure, and therefore absorption could not be quantitated.

Twelve out of 30 workers in a chemical manufacturing facility which produced silver nitrate and silver oxide were found to have blood silver levels greater than the detection limit of 0.6 μg silver/100 mL blood (Rosenman et al. 1979). Exposure levels were estimated to range from 0.039 to 0.378 mg silver/m^3. DiVincenzo et al. (1985) examined the silver content of blood, urine, and feces of workers exposed to TWA levels of 0.001 to 0.1 mg/m^3 insoluble silver in a photographic materials manufacturing facility. The identity of the specific silver compounds to which the workers were exposed was not reported. In exposed workers, silver was detected in 80% of the blood samples and in 100% of the fecal samples (mean concentrations of 0.011 μg/ml and 15 μg/g, respectively). Silver was detected in 2 of 35 (6%) urine samples from exposed workers with a mean concentration of 0.009 μg/g. Silver was also detected in the feces of controls (not exposed occupationally) at a mean concentration of 1.5 μg/g. Although these studies suggests that silver compounds are absorbed from the lungs, unknown exposure levels and lack of compound identification prevent estimation of extent or rate.

A study in dogs indicates that absorption of inhaled metallic silver particles with a median aerodynamic diameter of approximately 0.5 μm is extensive, and is not dependent upon particle size (Phalen and Morrow 1973). Absorption was measured in one dog that remained anesthetized during the entire period between exposure and sacrifice. In this dog, 3.1% (0.8 μg) of the deposited material was dissolved, transported out of the lungs, and was found mostly in liver and blood 6 hours after exposure; a 1 μg/cm^2/day absorption rate for metallic silver was estimated by the authors. up to 90% of the deposited silver was estimated to be absorbed into the systemic circulation based on all experimental data. Clearance from the lung to the blood was triphasic, with half-lives of 1.7, 8.4, and 40 days.

2.3.1.2 Oral Exposure

Based on medical case studies and experimental evidence in humans, many silver compounds, including silver salts and silver-protein colloids, are known to be absorbed by humans across mucous membranes in the mouth and nasal passages, and following ingestion. Absorption of silver acetate occurred following ingestion of a 0.08 mg/kg/day dose of silver acetate containing radiolabeled silver (^{110m}Ag). Approximately 21% of the dose was retained in the body at 1 week (East et al. 1980; MacIntyre et al. 1978). Furthermore, the occurrence of generalized argyria in a woman who repeatedly applied silver nitrate solution to her gums (Marshall and Schneider 1977) suggests that absorption across the oral mucosa can occur. Information concerning the rate of oral absorption in humans was not located.

The extent of absorption of an administered dose has been found to be associated with transit time through the gastrointestinal tract; the authors report that this may explain some of the interspecies differences in silver retention observed 1 week after exposure (see Table 2-3). The faster the transit time, the less silver is absorbed (Furchner et al. 1968). Transit times vary from about 8 hours in the mouse and rat to approximately 24 hours in the monkey, dog, and human (Furchner et al. 1968).

2.3.1.3 Dermal Exposure

Several silver compounds appear to be absorbed through the intact skin of humans, although the degree of absorption is thought to be low. For example, silver thiosulfate penetrated the intact skin of a photochemical worker via the eccrine sweat glands and deposited in the dermis, leading to the development of localized argyria within 6 months of exposure (Buckley 1963). Silver compounds also are absorbed through the damaged skin of humans. Silver was detected in the urine, blood, and body tissues of humans with seriously burned skin following treatment with topical preparations containing 0.5% silver nitrate to prevent bacterial infection (Bader 1966). The levels of silver found in one of the individuals studied by Bader (1966) were 0.038 and 0.12 ppm for urine and blood, respectively, and ranged from below detection in lung and brain to 1,250 ppm in skin. Snyder et al. (1975) estimated that less than 1% of dermally-applied silver compounds are absorbed through the intact skin of humans.

Absorption of silver nitrate across intact skin has been demonstrated in guinea pigs and is similar to that of intact human skin (Wahlberg 1965). The amount absorbed was estimated to be approximately 1% of the applied dose within 5 hours of exposure. Silver administered in the form of silver sulphadiazine cream was minimally absorbed through both the intact and burned skin of rats and distributed throughout the body (Sano et al. 1982). The absorption of silver increased through burned skin after blister removal. The authors did not determine the percentage of the applied dose that was absorbed (Sano et al. 1982).

TABLE 2-3. Interspecies Differences in the Oral Absorption of Silver

Species	Silver Compound	Body Weight (g)	Administered Dose (mg/kg)	Dose Retention at 1 Week (%)
Mouse[a]	$^{110m}AgNO_3$	26.6	0.0011[c]	<1
Rat[a]	$^{110m}AgNO_3$	355.0	0.0002[c]	≤1
Monkey[a]	$^{110m}AgNO_3$	6,730.0	0.00001[c]	<1
Dog[a]	$^{110m}AgNO_3$	13,330.0	0.000005[c]	≈10
Human[b]	$AgCH_3CO_2$	58,600.0	0.08	21

[a]Furchner et al. 1968.
[b]MacIntyre et al. 1978.
[c]Dose conversion: Specific activity was 8.7 Ci/g silver nitrate
8.7 Ci/g = 8.7 x 10^6 μCi/1 x 10^3 mg = 8,700 μCi/mg.

Administered dose (μCi)/8,700 μCi/mg = mg silver nitrate
mg silver nitrate/kg body weight/day = mg/kg/day.

Mouse: 0.25/8,700 = 2.87 x 10^{-5} mg silver nitrate
2.87 x 10^{-5} mg/0.0266 kg/day = 0.001 mg/kg/day.

Rat: 0.5/8,700 = 0.0001 mg silver nitrate
0.0001mg/0.355 kg/day = 0.0002 mg/kg/day.

Monkey: 0.6/8,700 = 0.0001 mg silver nitrate
0.0001 mg/6.73 kg/day = 0.00001 mg/kg/day.

Dog: 0.6/8,700 = 0.0001 mg silver nitrate
0.0001 mg/13.33 kg/day = 0.000005 mg/kg/day.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

Limited information was located concerning the distribution of silver in humans following inhalation of elemental silver or silver compounds. Using whole-body spectrometer measurements obtained from a person accidently exposed to radiolabeled silver, Newton and Holmes (1966) estimated that 25% of the detectable ^{110m}Ag was distributed to the liver between 2 and 6 days after exposure.

Phalen and Morrow (1973) reported that 96.9%, 2.4%, and 0.35% of the dose initially deposited in the lungs of a dog following intratracheal administration was detected in the lungs, liver, and blood, respectively, 6 hours after exposure. The remaining silver was detected in the gall bladder and bile (0.14%), intestines (0.10%), kidneys (0.06%), and stomach (0.02%). The distribution of metallic silver (expressed as a percentage of the initial amount deposited) 225 days after exposure differed from that at 6 hours, with the majority of the metal detected in the liver (0.49%), brain (0.035%), gall bladder and bile (0.034%), intestines (0.028%), lungs and trachea (0.019%), bone (0.014%), stomach and contents (0.012%), heart (0.009%), and muscle (0.007%). The distribution to tissues other than the lungs is similar at 6 hours and 225 days if silver in the lungs is not considered. At both time points the majority of the silver is found in the liver (approximately 77% of the total body silver excluding lung content).

2.3.2.2 Oral Exposure

The distribution of silver to various body tissues depends upon the route and quantity of silver administered and its chemical form. An oral dose of silver, following absorption, undergoes a first pass effect through the liver resulting in excretion into the bile, thereby reducing systemic distribution to body tissues (Furchner et al. 1968). The subsequent distribution of the remaining silver is similar to the distribution of silver absorbed following exposure by the inhalation and dermal routes and following intramuscular or intravenous injection.

Silver distributes widely in the rat following ingestion of silver chloride (in the presence of sodium thiosulfate) and silver nitrate in drinking water (at 88.9 mg silver/kg/day for silver nitrate) (Olcott 1948); The amount of silver in the various tissues was not measured, although qualitative descriptions of the degree of pigmentation were made. High concentrations were observed in the tissues of the reticuloendothelial system in the liver, spleen, bone marrow, lymph nodes, skin, and kidney. Silver was also distributed to other tissues including the tongue, teeth, salivary glands, thyroid, parathyroid, heart, pancreas, gastrointestinal tract, adrenal glands, and brain. Within these tissues advanced accumulation of silver

particles was found in the basement membrane of the glomeruli, the walls of blood vessels between the kidney tubules, the portal vein and other parts of the liver, the choroid plexus of the brain, the choroid layer of the eye, and in the thyroid gland (Olcott 1948; Moffat and Creasey 1972; Walker 1971).

Approximately 18-19% of a single oral dose of silver acetate was retained in the body of a human 8-30 weeks after exposure (East et al. 1980; Macintyre et al. 1978). This amount is 10% greater than that retained in dog tissues 20 weeks after a single oral dose (Furchner et al. 1968).

2.3.2.3 Dermal Exposure

Following the topical application of silver nitrate for the treatment of burns in two humans, silver was distributed to the muscles (0.03-2.3 ppm), liver (0.44 ppm), spleen (0.23 ppm), kidney (0.14 ppm), heart (0.032-0.04 ppm), and bones (0.025 ppm) (Bader 1966). No studies were located that quantitated the distribution of silver in animals following dermal exposure to silver or its compounds. However, Sano et al. (1982) detected silver in the same tissues of rats following topical application of silver sulphadiazine cream.

2.3.2.4 Other Routes of Exposure

In rats, silver was unevenly distributed in organs and tissues following intravenous or intramuscular injection of radiolabeled metallic silver and/or silver nitrate, respectively. The highest concentrations were found, in decreasing order, in the gastrointestinal tract, liver, blood, kidney, muscle, bone, and skin following intramuscular injection (Scott and Hamilton 1950). Following intravenous injection the highest concentrations were found, in decreasing order, in the liver, pancreas, spleen, and plasma (Klaassen 1979a). As is shown in Table 2-4, the proportion of the dose distributed to the tissues is positively correlated with the dose administered (Scott and Hamilton 1950).

Silver is cleared from the system via the liver (Furchner et al. 1968; Scott and Hamilton 1950). Deposition of uncleared silver can occur along the renal glomerular basement membrane (Creasey and Moffat 1973; Danscher 1981; Ham and Tange 1972; Moffat and Creasey 1972) and mesangium (Day et al. 1976), and in the Kupffer cells and the sinusoid endothelium cells of the liver (Danscher 1981). Silver has also been detected intra- and extracellularly in the skin and mucosa of the tongue, in the chromaffin cells, cells of the zona glomerulosa, and zona fasciculata of the adrenal glands, and in the exocrine and endocrine sections of the pancreas (Danscher 1981).

In rodents, silver has been shown to cross the placenta and to enter the fetuses following an intraperitoneal injection of silver lactate to the mothers (Rungby and Danscher 1983a). Silver was detected in the liver and brain tissues of rat fetuses (Danscher 1981; Rungby and Danscher 1983a).

TABLE 2-4. Distribution in Rats at Six Days of Intramuscularly Administered Radioactive Silver Tracer Dose when Administered Alone and when Coadministered with Additional Silver as Silver Nitrate

	Percent of Tracer Dose Recovered		
Tissue	Tracer Dose Alone	Silver Nitrate 0.4 mg/kg/day	Silver Nitrate 4.0 mg/kg/day
Heart and lungs	0.06	0.13	0.59
Spleen	0.01	0.13	2.69
Blood	0.5	0.95	3.03
Liver	0.36	2.24	33.73
Kidney	0.07	0.92	0.63
Gastrointestinal tract	1.12	4.22	8.21
Muscle	0.27	0.56	2.39
Bone	0.18	0.35	2.20
Skin	0.24	0.67	7.39
Urine	0.64	0.88	1.82
Feces	96.56	88.95	37.33

note: A small (unspecified) dose of radioactively labeled silver was used as a tracer. The distribution of silver is reported as percentage of tracer dose radioactivity recovered per organ.

Source: Scott and Hamilton 1950

2.3.3 Metabolism

The deposition of silver in tissues is the result of the precipitation of insoluble silver salts, such as silver chloride and silver phosphate. These insoluble silver salts appear to be transformed into soluble silver sulfide albuminates, to bind to or form complexes with amino or carboxyl groups in RNA, DNA, and proteins, or to be reduced to metallic silver by ascorbic acid or catecholamines (Danscher 1981). The blue or gray discoloration of skin exposed to ultraviolet light in humans with argyria may be caused by the photoreduction of silver chloride to metallic silver. The metallic silver is then oxidized by tissue and bound as black silver sulfide (Danscher 1981). Buckley et al. (1965) identified silver particles deposited in the dermis of a woman with localized argyria as being composed of silver sulfide.

In rats, silver deposits in internal organs such as the kidney, have also been identified as the sulfide (Berry and Galle 1982). Under conditions of exposure to high doses of selenium, the sulfur can be replaced by selenium (Berry and Galle 1982). The deposition of silver in the kidney was increased under conditions of high selenium exposure. This may be important in the development of argyria in people exposed to silver who ingest foods that contain large amounts of selenium (See Section 2.7).

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

The clearance of radioactive silver metal dust in a man who was accidentally exposed illustrated the rapid removal of silver from the lungs primarily by ciliary action, with subsequent ingestion and ultimate elimination in the feces (Newton and Holmes 1966). Lung clearance fit a biexponential profile, with biological half-lives of 1 and 52 days. Radioactive silver was detected in the feces up to 300 days after exposure, but was not detected in urine samples (collected up to 54 days after exposure).

Chronic exposure of workers to unidentified silver compounds resulted in the detection of silver in 100% of the fecal samples and 6% of the urine samples (DiVincenzo et al. 1985). This occupational exposure is assumed to have occurred primarily by the inhalation route.

In dogs, lung clearance of metallic silver particles (average aerodynamic diameter of 0.5μ) following intra-tracheal intubation was accompanied by an increase in silver concentration in the area of the stomach and liver. The increase in silver concentration in the stomach suggests that some proportion of the silver particles are cleared by the mucociliary escalator and swallowed. However, the predominant route of clearance from the lung appeared to be through dissolution of the silver and transport through the blood. The

silver was apparently carried by the blood to the liver, with little cleared via the mucociliary passages (Phalen and Morrow 1973). Approximately 90% of the inhaled dose was excreted in the feces within 30 days of exposure. Clearance of deposited silver particles from the lung fit a triexponential profile, with biological half-lives of 1.7, 8.4, and 40 days, accounting for 59, 39, and 2% of the radioactivity excreted, respectively. Clearance of absorbed silver from the liver fit a biexponential profile with biological half-lives of 9.0 and 40 days accounting for 97% and 3% of the radioactivity excreted, respectively (Phalen and Morrow 1973).

2.3.4.2 Oral Exposure

Following oral exposure to silver acetate in humans, silver is eliminated primarily in the feces, with only minor amounts eliminated in the urine (East et al. 1980). The rate of excretion is most rapid within the first week after a single oral exposure (East et al. 1980). Whole-body retention studies in mice and monkeys following oral dosing with radiolabeled silver nitrate indicate that silver excretion in these species follows a biexponential profile with biological half-lives of 0.1 and 1.6 days in mice and 0.3 and 3 days in monkeys. In similarly exposed rats and dogs, silver excretion followed a triexponential profile with biological half-lives of 0.1, 0.7, and 5.9 days in rats and 0.1, 7.6, and 33.8 days in dogs (Furchner et al. 1968). Data for whole body clearance of silver at two days after exposure for these four species are presented in Table 2-5 (Furchner et al. 1968). Transit time through the gut may explain some of these interspecies differences in silver excretion. Transit time is approximately 8 hours in mice and rats, and approximately 24 hours in dogs and monkeys (Furchner et al. 1968). Animals excrete from 90% to 99% of an administered oral dose of silver in the feces within 2 to 4 days of dosing (Furchner et al. 1968; Jones and Bailey 1974; Scott and Hamilton 1950). Excretion in the feces is decreased and deposition in tissues, such as the pancreas, gastrointestinal tract, and thyroid, is increased when saturation of the elimination pathway in the liver occurs as a result of chronic or high level acute exposure to silver (see Table 2-4) (Constable et al. 1967; Olcott 1948; Scott and Hamilton 1950).

2.3.4.3 Dermal Exposure

No studies were located concerning the excretion of silver by humans or animals following dermal exposure to elemental silver or silver compounds. Once absorption through the skin and distribution to bodily tissues occurs, it can be expected that elimination would be similar to that of silver absorbed via oral or inhalation exposure, that is, primarily via the feces, with minimal amounts excreted in the urine.

2.3.4.4 Other Routes of Exposure

Whole body retention studies in mice, rats, monkeys, and dogs following intravenous injection of radiolabeled silver nitrate indicate that silver

excretion in these species follows a triexponential profile. (Furchner et al. 1968). For mice and monkeys, this differs from the biexponential profile seen following oral exposure. Whole body clearance following intravenous exposure was slower than clearance following oral exposure in each of the four species observed. In addition, the difference in clearance rate between species was more dramatic. Clearance at 2 days post-exposure ranged from 15% in the dog to 82% in the mouse (see Table 2-5) (Furchner et al. 1968).

Silver removal from the liver by biliary excretion was demonstrated by Scott and Hamilton (1950). Control rats and rats with ligated bile ducts were administered radioactive metallic silver by intramuscular injection. In rats with ligated bile ducts, excretion of silver in the feces was 19%, compared to 97% in controls. Deposition in the liver of rats with ligated bile ducts was 48% and 2.5% in the gastrointestinal tract compared to 0.36% and 1.12%, respectively in the controls (Scott and Hamilton 1950). Klaassen (1979b) determined that biliary excretion accounted for between 24% and 45% of the silver administered to rats. The concentration of silver in the bile was estimated to be between 16 and 20 times greater than that in plasma. An increase in the bile/liver tissue ratio (μg/ml per μg/g) from 4.2 to 6.4 indicates that more silver is concentrated in the bile as the dose of silver increases. It is believed that active transport is involved in the transfer of silver from the plasma to the bile (Klaassen 1979b). There are apparently interspecies differences in this transport process. The variability in the extent of biliary silver excretion appears to be related to the ability of the liver to excrete silver into the bile, not to the ability of the silver to pass between the plasma and the liver. Rats excreted silver in the bile at 10 times the rate of rabbits. Dogs excreted silver in the bile at a rate lower than that of rabbits (Klaassen 1979b). Dogs had the highest amount of silver retained in the liver (2.9 μg silver/g), as compared to the rabbit (2.13 ,μg silver/g) and rat (1.24 μg silver/g).

2.4 RELEVANCE TO PUBLIC HEALTH

The one clinical condition that is known in humans to be attributable to long-term exposure to silver and silver compounds is a gray or blue-gray discoloring of the skin (argyria). Argyria may occur in an area of repeated or abrasive dermal contact with silver or silver compounds, or more extensively over widespread areas of skin and the conjunctiva of the eyes following long-term oral or inhalation exposure. Argyria was common around the turn of the century when many pharmaceutical preparations contained silver (Hill et al. 1939). It is much less common today, probably because most current medications containing silver are for dermal application only. Case reports in humans have reported that repeated dermal contact with silver compounds may in some cases lead to contact dermatitis, and a generalized allergic reaction to silver.

Evidence from both human and animal studies indicates that inhalation of silver compounds can irritate the respiratory pathway. Occupational studies

TABLE 2-5. **Interspecies Differences in the Clearance of Silver Compounds**[a]

Species	Silver Compound	Route	Dose (mg/kg/day)	% of Dose Cleared at 2 Days
Mouse	$^{110m}AgNO_3$	Oral	0.0011	99.61
		Intravenous	0.0010	82.08
Rat	$^{110m}AgNO_3$	Oral	0.0002	98.35
		Intravenous	0.0002	70.73
Monkey	$^{110m}AgNO_3$	Oral	0.00001	94.35
		Intravenous	0.00001	44.08
Dog	$^{110m}AgNO_3$	Oral	0.000005	90.38
		Intravenous	0.000003	15.00

[a]Furchner et al. 1968.

Dose conversion: Specific Activity was 8.7 Ci/g Silver nitrate
8.7 Ci/g = 8.7 x 10^6 μCi/1 x 10^3 mg = 8700 μCi/mg
μCi/μCi/mg=mg; mg/kg/day=dose

Dose Calculation:

Mouse: oral: 0.25 μCi/wt=26.5g: 0.25/8700=2.87 x 10^{-5}/0.0265 = 0.0011 mg/kg/day
iv: 0.25 μCi/wt=27.4g: 0.25/8700=2.87x10^{-5}/0.0274 = 0.0010 mg/kg/day
Rat: oral: 0.5 μCi/wt=355g: 0.5/8700=0.0001/0.355=0.0002 mg/kg/day
iv: 0.5 μCi/wt=369g: 0.5/8700=0.0001/0.369=0.0002 mg/kg/day
Monkey:oral: 0.6 μCi/wt=6730g: 0.6/8700=0.0001/6.73=0.00001 mg/kg/day
iv: 0.6 μCi/wt=6880g: 0.6/8700=0.0001/6.88=0.00001 mg/kg/day
Dog: oral: 0.6 μCi/wt=13330g: 0.6/8700=0.0001/13.33=0.000005 mg/kg/day
iv: 0.4 μCi/wt=14400g: 0.4/8700=0.000046/14.40=0.000003 mg/kg/day

and reports of cases where individuals have accidentally swallowed solutions of silver nitrate show that both inhalation and ingestion may cause gastric discomfort as well.

Studies in humans and animals indicate that silver compounds are absorbed readily by the inhalation and oral routes and poorly by the dermal route, and are distributed widely throughout the body. Observations made during surgery on silver exposed individuals and histopathologic studies of animals exposed to silver compounds demonstrate that within certain tissues of the body (most notably liver, kidney, pancreas, skin, conjunctiva of the eyes, and, to a lesser degree, certain brain areas) silver is deposited in the form of granules visible with the light microscope. However, with the exception of one report of decreased activity in mice exposed to silver nitrate, and one report of enlarged hearts in rats exposed to silver nitrate or silver chloride, there is no evidence that suggests that the silver deposits might interfere with the normal functioning of these organs in humans.

Death. There is no information concerning death in humans following exposure to silver compounds by any route.

Data concerning death observed in animals following oral and dermal exposure to silver compounds suggest that levels of exposure would have to be quite high to cause death in humans. High levels of colloidal silver were observed to cause death in rats when administered in drinking water for acute and intermediate exposure durations. The cause of death was unknown. The corresponding daily oral dose for a 70-kg man based on the dose levels tested would be approximately 12 grams. Death caused by silver has not been observed to occur in humans or animals following dermal exposure to silver compounds, nor is it expected to occur.

Systemic Effects. Silver nitrate and/or silver oxide have been reported to cause upper and lower respiratory tract irritation in humans when inhaled. In one case, inhalation of an unknown amount and chemical form of silver during work with molten silver ingots produced respiratory failure the day after exposure (Forycki et al. 1983). Without treatment the worker may have died. However, exposures such as this are not expected to be common and should be examined on a case by case basis.

Upper respiratory irritation has been observed in humans at estimated exposure levels of between 0.039 and 0.378 mg silver/m^3 for less than 1 to greater than 10 years. Evidence that silver colloid can act as an irritant is provided by the fact that ultrastructural damage was seen in the tracheal epithelium of rabbits following inhalation exposure to an unknown concentration of silver colloid. However, these effects are likely to be related to the caustic properties of the compounds, not to the presence of silver. The effects are not expected to persist when exposure to air containing silver compounds has stopped.

The same exposure conditions can also cause gastric discomfort in humans. Again, this effect is likely to be caused by the caustic effects of the silver compounds, and not the presence of silver. There is no evidence that suggests that dermal exposure to silver can cause gastric effects.

Occupational exposure to silver compounds has not been observed to affect blood counts. Although no supportive studies were located regarding hematological effects in other species or by other routes, the occupational exposure findings suggest that hematological effects are not a sensitive indicator of silver toxicity.

Silver is deposited in the glomerular basement membrane of the kidney of animals, and therefore might be expected to affect renal function. However, no studies of renal function in animals were located, and occupational studies in humans are not adequate for establishing a clear relationship between exposure to silver and renal impairment.

No human studies were located that indicate that exposure to silver or silver compounds will affect the cardiovascular system. However, an animal study did show an increase in the relative size of the left ventricle of rats that had been chronically exposed to silver nitrate or silver chloride in drinking water. Despite the suggestion by the authors that the increase in left ventricle size may be caused by vascular hypertension, 'this effect has not been observed in animals or in humans. These endpoints have not been specifically addressed in reliable studies to date.

The predominant effect of exposure to silver in humans is the development of a characteristic, irreversible pigmentation of the skin. This condition is called argyria. Clinicians describe the pigmentation as slate-gray, bluegray, or gray in color and report it as most noticeable in areas of skin exposed to light. The pigmentation is not a toxic effect per se, nor is it known to be diagnostic of any other toxic effect. However, the change in skin color can be severe enough to be considered a cosmetic disfigurement in some cases.

The discoloring is likely to be caused by the photoreduction of silver chloride and/or silver phosphate in the skin. X-ray dispersive analysis of skin and other tissues reveals that the granules consist of silver complexed with sulfur and/or selenium. The photoreduced deposits are not removed by the body, and there are no clinical means of removing them.

Levels of silver exposure that have led to argyria in humans in the past are poorly documented, and it is not possible to establish minimum risk levels for this effect based on these data. Hill and Pillsbury (1939) in their review of cases of argyria report that total doses of silver that have resulted in argyria can be as low as a total of 1.4 grams of silver (as silver nitrate) ingested in small unspecified doses over several months.

An animal model for studying the pigmentation changes seen in humans does not exist. Therefore existing experimental animal data are of limited use in predicting the exposure levels that would result in argyria in humans. Granular deposits that contain silver have been observed in both pigmented and unpigmented skin of silver-exposed humans. Similar granules have been observed in various tissues in animals following silver exposure (see Section 2.2 and below). However, a direct correlation has not been established between the granular deposits seen in animals following exposure to silver and the deposition leading to skin discoloration in humans.

Immunological Effects. No studies were located that investigated toxic effects on the immune system in humans or animals exposed to silver, or that indicate that immune-related disease can be affected by silver exposure. Silver has been observed to elicit a mild allergic response (contact dermatitis) in humans following dermal exposure to various silver compounds.

Neurological Effects. Neurological effects attributable to silver have not been reported in humans nor have existing case or occupational studies focused on this endpoint. Exposure to silver has been observed to result in the deposit of silver in neurons of the central nervous system of a woman who had used nasal drops containing silver nitrate and in animals exposed by intraperitoneal injection and through drinking water. However, this effect is not known to be toxic. As measured using a controlled, blind assay, the activity of mice with silver deposits in their brain was less than that of controls. The decrease in activity could be attributable to other factors unrelated to central nervous system function (such as loss of appetite due to gastric effects, or general malaise) and the relevance to humans is not known.

Exposure to silver has been observed to affect the volume of hippocampal cell groups within the brain of animals. Several cell groups within the hippocampus (a well defined structure of the brain involved in some aspects of memory) are reduced in overall volume in rats exposed during their first 4 weeks of life to subcutaneously injected silver lactate (0.137 mg silver/kg/day) (Rungby et al. 1987). Unfortunately, the study is limited in that only one small region of the brain was examined. It is prudent to assume that similar effects would be observed in humans; however, the implications of the altered volume of these cell groups are not known.

Developmental Effects. Based on the existing information, it is not known whether silver causes developmental toxicity in humans. No studies were found concerning developmental effects in humans after exposure to silver. However, a human study by Robkin et al. (1973) did investigate the possibility of a relationship between the concentration of this heavy metal in the tissue of fetuses and the occurrence of developmental abnormalities. These authors reported that the concentration of silver in the fetal liver of 12 anencephalic human fetuses was higher (0.75±0.15 mg/kg) than the values from 12 fetuses obtained either through therapeutic abortions

(0.23±0.05 mg/kg), or in 14 spontaneously aborted fetuses (0.21±0.05 mg/kg). The concentration in 9 premature infants was 0.68±0.22 mg/kg. The authors could not determine if the higher concentrations of silver in anencephalic fetuses were associated with the malformation, or with fetal age.

Silver has been demonstrated in the brains of neonatal rats whose mothers received injections of silver lactate on days 18 and 19 of gestation (Rungby and Danscher 1984). As mentioned above, treatment of neonatal rats has also been found to reduce the volumes of certain cell groups within the hippocampus (Rungby et al. 1987). However, functional tests were not performed on these rats, and therefore, neither the significance of the silver accumulation, nor the decrease in regional hippocampal volume can be determined.

Reproductive Effects. The existing evidence does not point to a strong effect of silver on reproduction. However, no multigeneration reproductive studies were located, and therefore a firm conclusion regarding reproductive toxicity can not be made.

There is no historical evidence in humans to suggest that silver affects reproduction, although studies specifically designed to address this endpoint in humans were not located. One study in five male rats found that single subcutaneous injections of 0..04 millimole/kg silver nitrate caused temporary histopathological damage to testicular tissue (Hoey 1966). Eighteen hours after a single injection, silver caused shrinkage, edema, and deformation of the epididymal tubules. All affected tissues showed gradual recovery from damage following the initial injection, in spite of continued daily injections. Although treatment over a 30-day period had no effect on spermatogenesis, spermatozoa were observed with separated and pyknotic heads. A separate drinking water study in male rats did not observe changes in spermatozoa or diminution in fertility.

Finally, direct intrauterine injection of silver nitrate terminated pregnancies in monkeys (Dubin et al. 1981). Single dose intrauterine injections of 1% silver nitrate solution (0.78 mg/kg) resulted in vaginal bleeding for 1 or 2 days following treatment. The bleeding lasted for an average of 5.3 days. Pregnancy was terminated in all these cases. In subsequent pregnancies, these monkeys produced normal offspring. The relevance of direct uterine injection to human exposure conditions from NPL site contamination must be evaluated on a case by case basis since this effect has not been studied by the more common exposure pathways.

Genotoxic Effects. No studies were located that examined the mutagenicity or genotoxicity of silver in human cells in vivo or in vitro. Existing data on mutagenicity are inconsistent, but data on genotoxicity suggest that the silver ion is genotoxic. Table 2-6 presents the results of in vitro genotoxicity studies using bacteria and nonhuman mammalian cell cultures. From these studies and others it is evident that the silver ion

does bind with DNA in solution in vitro, and that it can interact with DNA in ways that cause DNA strand breaks and affect the fidelity of DNA replication (Goff and Powers 1975; Loeb et al. 1977; Luk et al. 1975; Mauss et el. 1980; Robison et al. 1982; Scicchitano and Pegg 1987). However, silver has not been found to be mutagenic in bacteria (Demerec et al. 1951; Kanematsu et al. 1980; McCoy and Rosenkranz 1978; Nishioka 1975; Rossman and Molina 1986).

Cancer. No studies were located regarding cancer in humans following inhalation, oral, or dermal exposure to silver or silver compounds. Fibrosarcomas have been induced in rats following subcutaneous imbedding of silver foil (Oppenheimer et al. 1956). In this study, imbedded silver metal foils appeared to produce fibrosarcomas earlier (latent period as short as 275 days compared to 364-714 days) and more frequently (32% of implantation sites compared to O-S%) than other metal foils (steel, tantalum, tin, and vitallium) tested. However, experiments on several metals (steel, tantalum, and vitallium) were not complete at the time of publication so adequate comparisons could not be made. In addition, it should be noted that several material are known to regularly produce such tumors when implanted subcutaneously in animals, and the relevance to carcinogenesis in humans is uncertain (Coffin and Palekar 1985). Both positive (Schmahl and Steinhoff 1960) and negative (Furst and Schlauder 1977) results for tumorigenesis have been reported following subcutaneous and intramuscular injection, respectively, of colloidal silver in rats. However, the relevance of these routes of exposure to exposure conditions at hazardous waste sites has not been clearly established. Animal toxicity and human occupational studies using normal routes of exposure have not provided indications of carcinogenicity, and silver is not expected to be carcinogenic in humans.

2.5 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule or cell that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time biologic samples can be

TABLE 2-6. Genotoxicity of Silver In Vitro

End Point	Species (Test System)	Results: With Activation	Results: Without Activation	Reference
Prokaryotic organisms:				
Gene mutation	Escherichia coli	ND	-	Demerec et al. 1951
	Salmonella typhimurium (strains TA1535, 1537, 1538, and 100)	-	-	McCoy and Rosenkranz 1978
	E. coli (enhancement of UV-light induced mutagenesis)	ND	-	Rossman and Molina 1986
	E. coli	ND	-	Kanematsu et al. 1980
	E. coli	ND	-	Nishioka 1975
	Photobacterium fischeri	ND	(+)	Ulitzur and Barak 1988
Eukaryotic organisms:				
DNA damage	Chinese hamster ovary cells (DNA strand breaks)	ND	+	Robinson et al. 1982
Viral transformation	Syrian hamster embryo	ND	+	Casto et al. 1979
DNA effects:				
Replication fidelity	Synthetic DNA	ND	+	Loeb et al. 1977

ND = no data; - = negative; (+) = weakly positive; + = positive.

taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc and selenium). Biomarkers of exposure to silver are discussed in Section 2.5.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are often not substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by silver are discussed in Section 2.5.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, biologically effective dose, or target tissue response. If biomarkers of susceptibility e xist, they are discussed in Section 2.7, "POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE."

2.5.1 Biomarkers Used to Identify or Quantify Exposure to Silver

Silver can be detected in blood, urine, feces, hair, and biopsy specimens using standard analytic techniques, as well as whole body analysis using in vivo neutron activation. The presence of silver in these samples can be used, with varying degrees of accuracy depending on the sample, as a biomarker of exposure to silver compounds. Analysis of hair has been used to monitor for silver exposure (DiVincenzo et al. 1985). However, silver can be adsorbed onto hair surfaces as well as deposited during hair formation, and since current testing procedures cannot differentiate between the two modes, hair monitoring is an unreliable biomarker of exposure (DiVincenzo et al. 1985). Levels of silver in feces, blood, and urine have been associated with recent exposure via inhalation, oral, and dermal routes. Levels in these biological media may serve as more reliable, primary biomarkers of exposure to silver than levels in hair (DiVincenzo et al. 1985; Rosenman et al. 1979, 1987). These biomarkers appear to be independent of the route of exposure, but have not been quantitatively correlated with level and duration of exposure. The prevalence and estimated magnitude of silver deposition in the skin, however, were associated with duration of occupational exposure.

Because silver is eliminated primarily through the feces, recent exposure is most easily monitored through fecal analysis. Measurements of silver in the blood are also significant and indicate exposure to the metal. However,

silver is not always detected in the urine samples of workers with known exposure to the chemical, and is not as reliable a biomarker as feces and blood. DiVincenzo et al. (1985), for example, detected silver in 100% of feces samples and only 6% of urine samples from workers chronically exposed to silver compounds in air. Increased blood silver levels, above the detection limit for silver (0.6 μg/l00 mL blood), have been associated with inhalation exposure to the metal in a study by Rosenman et al. (1979).

Levels in biopsy specimens (e.g., of skin) provide information concerning repeated exposure (Blumberg and Carey 1934; East et al. 1980). After a burn victim had been dermally exposed to silver nitrate (as a bactericidal agent), Bader (1966) found silver primarily in the patient's skin as well as in the blood and urine. Further information can be found in Section 2.3.

2.5.2 Biomarkers Used to Characterize Effects Caused by Silver

Several effects associated with silver exposure have been reported in humans which may be useful as biomarkers of effects. The significance of these biomarkers, however, is in doubt, because they do not appear consistently in exposed individuals and do not seem to correlate well with levels and duration of exposure.

One easily observed effect of silver exposure is argyria which is a slate-gray or blue-gray discoloration of the conjunctivae, cornea, skin, and other epithelial surfaces. Oral, inhalation, or dermal absorption of silver may cause argyria in humans. A potential biomarker of silver deposition that could lead to this effect would be the presence of insoluble silver salts (e.g., silver chloride, sulfide, or phosphate) in skin biopsy, especially that associated with basement membrane (Danscher 1981). The granular deposition of silver in the cornea of workers has been loosely associated with complaints of decreas.ed night vision (Moss et al. 1979; Rosenman et al. 1979). However, Pifer et al. (1989) studied various ophthalmological end points in workers exposed to silver and silver compounds and could find no significant ocular impairments associated with the metal.

Low oxygen content in capillary blood, scattered thickening of lungs (as observed in chest radiograms), and upper respiratory irritation have been observed in studies of workers exposed intensely or chronically to molten silver or silver dusts (Forycki et al. 1983; Rosenman et al. 1979, 1987). Inhalation exposure also led to decreased red blood cell count and an increased mean corpuscular volume (Pifer et al. 1989). However, these potential hematologic biomarkers are not specific for silver exposure, and do not indicate or predict significant clinical sequelae.

Rosenman et al. (1987) found that inhalation exposure to silver caused changes in two renal end points which could be biomarkers of mild nephrotoxicity. In this study exposed workers exhibited lower creatinine clearance and higher excretion of the urinary enzyme N-acetyl-β-D

glucoseaminidase. However, workers in the study were also exposed to cadmium, a known nephrotoxic agent, which may have been responsible for the observed changes. Therefore, these biochemical effects cannot be considered reliable biomarkers of silver exposure. Occupational exposure to silver nitrate and silver oxide, leading to blood silver levels above 0.6 μg/100 mL, correlated strongly with increased complaints of abdominal pain (Rosenman et al. 1979). Moreover, dermal exposure to silver and silver compounds has been associated with a mild allergic reaction in humans which may be a biomarker of immunological effects (Catsakis and Sulica 1978; Hey1 1979; Marks 1966). Please refer to Section 2.2 of Chapter 2 for a more detailed discussion of the effects caused by silver and its compounds.

2.6 INTERACTIONS WITH OTHER CHEMICALS

As with other metals, relationships exist through which silver can influence the absorption, distribution, and excretion of one or more other metals. These influences are not known to increase the toxicity of other metals, nor are other metals known to add to any toxic effects of silver.

However, high intake of selenium (e.g., as sodium selenite or selenium oxide) may lead to increased deposition of insoluble silver salts in body tissues through the formation of silver selenide (Alexander and Aaseth 1981; Berry and Galle 1982; Nuttall 1987). Exposure to silver nitrate in drinking water concurrent with intraperitoneal injections of selenium dioxide results in a higher rate of deposition of granular deposits in the kidneys of rats than that seen with exposure to silver nitrate alone (Berry and Galle 1982). Higher deposition rates are likely to accelerate the development of argyria, although no data were located to confirm this.

No other studies were located regarding additive or synergistic toxic interactions of silver with any other substance. However, exposure to moderate-to-high silver levels (130-1000 ppm) in rats with dietary deficiencies such as vitamin E alone (Bunyan et al. 1968; Grass0 et al. 1969) or vitamin E and selenium (Van Vleet 1976; Van Vleet et al. 1981) can cause moderate-to-severe liver necrosis.

It should be noted that selenium plays a dual role in the toxicity of silver. On the one hand, it increases the silver deposition rate in body tissues, which suggests that humans exposed to both high selenium and high silver may be more likely to develop argyria. On the other hand, a seleniumdeficient diet combined with high silver intake can cause liver necrosis.

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

Populations that are unusually susceptible to toxic effects of silver exposure are those that have a dietary deficiency of vitamin E or selenium, or that may have a genetically based deficiency in the metabolism of these essential nutrients. Individuals with damaged livers may also be more

susceptible to the effects of silver exposure. In addition, populations with high exposures to selenium may be more likely to develop argyria. Furthermore, some individuals may exhibit an allergic response to silver.

2.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of silver is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of silver.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.8.1 Existing Information on Health Effects of Silver

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to silver are summarized in Figure 2-2. The purpose of this figure is to illustrate the existing information concerning the health effects of silver. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs" information.

The majority of literature reviewed concerning the health effects of silver in humans described case reports of individuals who developed argyria following oral exposure to silver. Occupational studies describing two separate worker populations were also located. The predominant route of exposure in the occupational studies is believed to have been inhalation, but the possibility of some degree of oral or dermal exposure cannot be ruled out. Information on human exposure is limited in that the possibility of concurrent exposure to other toxic substances cannot be excluded, and the duration and level of exposure to silver generally cannot be quantitated from the information presented in these reports.

As can be seen in Figure 2-2, very little information exists on the effects of dermal or inhalation exposure to silver in animals. Despite the need to evaluate NPL site exposure on a case by case basis, these routes are not expected to be significant sources of silver exposure. Furthermore, the oral exposure route has been examined primarily in regards to silver

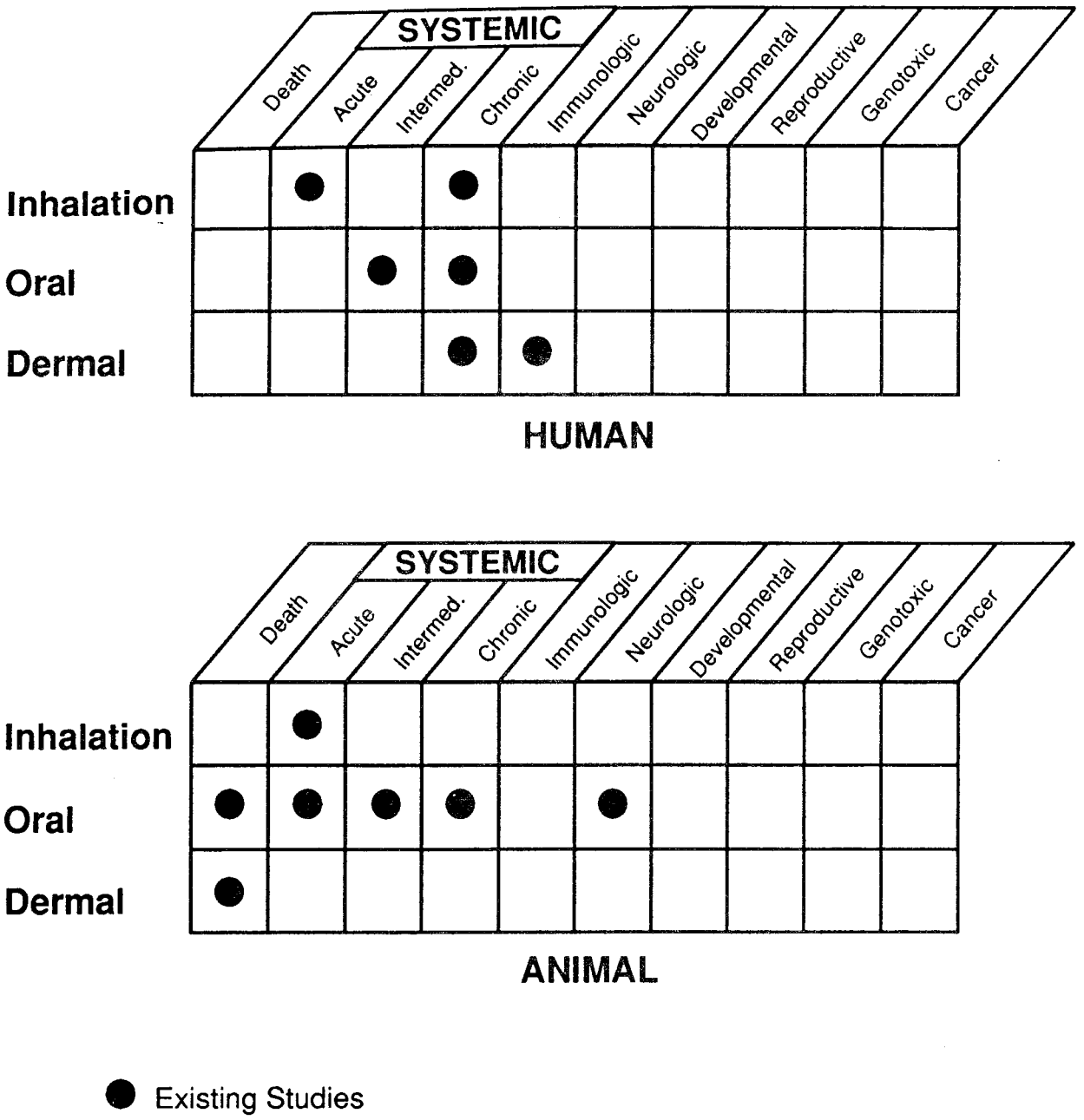

FIGURE 2-2. Existing Information on Health Effects of Silver

deposition in various tissues. The studies were not designed to examine other end points.

2.8.2 Identification of Data Needs

Acute-Duration Exposure. Information exists on the effects of acuteduration inhalation exposures to silver in humans and experimental animals. The information located is limited to one case report and an animal study that examined a single end point. Information concerning acute-duration exposure by the oral and dermal routes was not located. Insufficient data exist to establish a target organ or an MRL. Pharmacokinetic data that would support the identification of target organs across routes for acute-duration exposures were also not located. A more general data need is a comparative analysis of the toxicity of various silver compounds. Comparative toxicity data of silver compounds would allow a more accurate analysis of variations in toxicity caused by site-specific conditions, as may occur at NPL sites, or oxidizing and reducing conditions associated with specific exposure routes. Acuteduration exposure information would be useful because there may be populations adjacent to hazardous waste sites that might be exposed to silver for brief periods.

Intermediate-Duration Exposure. Information exists on the effects of intermediate dose exposures in both humans (inhalation and oral) and experimental animals (oral only). However, sufficient data do not exist to identify a target organ or establish an MRL for intermediate exposure durations. The exact duration and level of exposure in the human studies generally cannot be quantitated because the information is derived from anecdotal case reports rather than controlled epidemiological studies. Moreover, the animal studies predominantly describe deposition in the nervous system, eyes, and skin. One animal study has implicated the heart as a target organ. Controlled epidemiological studies in which exposure duration and level are quantified could be useful in identifying target organs in humans and for estimating the risk associated with intermediate-duration exposures. Additional animal studies investigating possible functional changes in organs in which silver deposition has been observed could also be used to identify possible health effects in humans. Animal studies that report deposition of silver in the skin employ intermediate or chronic exposure levels that are well above those estimated to cause argyria in humans. A reliable animal model of silver deposition rates and the occurrence of argyria may not be possible because of the photoreduction role that light plays.and the difficulty in providing similar conditions for laboratory animals. However, a dose-response study in which the deposition of silver in the skin is examined would be helpful in deriving MRLs for the development of argyria. Pharmacokinetic data that would support the identification of target organs across routes for intermediate-duration exposures were also not located. Little or no reliable information exists for other end points. Intermediateduration exposure information would be useful because there may be mobile or

migratory populations adjacent to hazardous waste sites that might be exposed to silver for similar durations.

Chronic-Duration Exposure and Cancer. No controlled epidemiological studies have been conducted in humans. Although argyria has been known to occur following chronic silver exposure, the general lack of quantitative information concerning this effect in humans or animals precludes the derivation of an MRL for this duration. Occupational studies weakly suggest that impairment of vision, gastrointestinal distress, or renal histopathology may result from chronic exposure to silver in humans. Additional information would be useful in confirming or denying these possibilities, and in establishing an MRL for chronic exposure. Pharmacokinetic data that would be useful in the identification of target organs or carcinogenic potential across routes for chronic duration exposures were also not located. Predominantly negative genotoxicity studies and the lack of reports of cancer associated with silver in humans, despite long-standing and varied usage, suggest that silver does not cause cancer. However, no chronic toxicity/carcinogenicity bioassays have been conducted in animals, and one study has reported an increase in tumors in rats following subcutaneous injections (the tumors occurred predominantly at the site of injection). A combined chronic toxicity/carcinogenicity study would be useful to address uncertainties in the database. Chronic-duration exposure information would be useful because there may be populations adjacent to hazardous waste sites that might be exposed to silver for long periods of time.

Genotoxicity. No studies were located that address the genotoxic effects of silver in humans. All information on silver genotoxicity comes from in vitro studies (predominantly microbial assays). These studies indicate that, while silver ions do interact with DNA in vitro, silver is not mutagenic. However, there is evidence that silver can cause DNA strand breaks and influence the fidelity of DNA replication. Better characterization of this evidence of genotoxicity, especially in in vivo test systems, would assist in the evaluation of silver genotoxicity.

Reproductive Toxicity. No information on the reproductive effects of silver in humans was located. Limited information in one study in laboratory animals suggests that chronic oral exposure to levels of silver high enough to cause widespread granular deposition has a low potential to induce adverse reproductive effects in either sex. However, this study did not examine all relevant reproductive end points. Furthermore, no studies were located that examined reproductive effects following silver exposure by inhalation or dermal routes. One subcutaneous injection study in animals demonstrated an effect on testicular tissue and sperm morphology (Hoey 1966). Examination of reproductive pathology in a go-day study would be useful to determine whether or not a multigeneration reproductive study is warranted to clarify the issue of reproductive effects of silver.

Developmental Toxicity. No information concerning developmental effects of silver in humans resulting from ingestion, inhalation, or dermal contact with silver was found. One study did investigate the relationship between silver levels in fetal tissue and the occurrence of deformities. However, a causal relationship was not established between exposure to silver and the deformities. Limited data in neonatal rats indicate that silver in drinking water can reduce the volume of certain well-defined brain regions. However, the functional significance of changes in volume of these small brain areas is not known. Data from pharmacokinetic studies that would support cross-route extrapolation were not located. Studies that further investigate the above end points for all routes of exposure would be useful to characterize the developmental effects of silver.

Immunotoxicity. Information on immunological effects of silver in humans is limited to clinical observations of allergic reactions to silver compounds after repeated dermal exposure in humans. No animal studies were located that examine immunologic end points, or that provide additional information regarding the allergic response to the silver ion. Information concerning the allergic potential of silver by the dermal, oral, and inhalation routes would be useful in identifying potential sensitive populations. A battery of immune function tests (e.g., ratio of T cells to B lymphocytes, levels of antibody classes, macrophage function, etc.) would be useful to determine whether silver compounds adversely affect the immune system.

Neurotoxicity. Existing studies show that silver can be deposited in anatomically defined regions of the brain .in both humans and animals following repeated oral exposure to silver. Other studies indicate that neuroanatomical changes can occur in young rats, and that the general activity level of exposed mice is less than that of unexposed mice. The significance of the neuroanatomical changes is not clear, and the study investigated only one small area that was not reported as an area of high silver deposition. Studies of the neuroanatomical areas that concentrate silver, and more specific neurobehavioral tests, would assist in defining the neurotoxic potential of silver for all routes of exposure.

Epidemiological and Human Dosimetry Studies. Most of the existing information on the effects of silver in humans comes from cases of individuals diagnosed with argyria following the intentional ingestion of medicinal silver compounds (silver nitrate and silver acetate) and from exposure of small numbers of worker populations in chemical manufacturing industries. Inherent study limitations include unquantified exposure concentrations and durations, as well as possible concomitant exposure to other toxic substances. Wellcontrolled epidemiological studies of communities living in close proximity to areas where higher than background levels of silver have been detected in soil and surface and/or groundwater, such as might occur near hazardous waste sites, and occupationally exposed groups would help supply information needed to clarify speculation regarding human health effects caused by silver.

Biomarkers of Exposure and Effect. Silver can be detected in blood, urine, feces, hair, and skin biopsy specimens. The best indictor of recent exposure to silver or silver compounds is detection of silver levels in feces and blood. Intermediate as well as long-term exposures are best monitored by measuring silver in blood or skin biopsy specimens. Argyria, the change in skin color associated with silver exposure, is also an indicator of chronic exposure. No other biomarkers for silver have been developed. Development of alternative biomarkers capable of detecting early exposure to low levels of silver would be useful in determining the possible toxic effects of this metal.

The only biomarkers of effect that have been reliably associated with silver exposure are argyria and granular deposits in the dermis and eyes. These are normally observed only in cases of intermediate and long-term exposure. Some clinical symptoms (e.g., gastrointestinal distress and respiratory discomfort) have been loosely associated with exposure, but are not definitive for exposure. No good quantitative correlations have been drawn between body levels of silver and these observed effects. Development of additional biomarkers of effect, especially for short-term and low-level silver exposure would be useful in determining the potential of silver to cause health impairment or disease. More information on the body burden of individuals with argyria, including skin biopsies, would help clinicians determine the risk of argyria for individuals with a history of silver exposure. If exposure levels of silver can be shown to correlate with specific adverse health effects, it may be possible to determine quantitative relationships between changes in tissue and/or body levels of silver.

Absorption, Distribution, Metabolism, and Excretion. The database for inhalation and dermal absorption of silver compounds in humans consists primarily of qualitative evidence from occupational case studies. Limited quantitative information exists on the oral absorption of silver compounds in humans. Research into the quantitative absorption of various silver compounds following relevant exposure routes would be useful to better predict the potential for toxic responses to particular silver compounds in humans.

Additional research into the comparative absorption, distribution, metabolism, and excretion of different silver compounds would allow a more accurate determination of the effects of silver exposure under specific environmental conditions. The current database primarily provides information concerning silver nitrate. Certain compounds that may exist at hazardous waste sites, such as silver oxide, silver thiosulfate, silver chloride, silver phosphate, and silver sulfide, have not been studied.

Studies were located for oral and dermal absorption in animals, but are lacking for absorption from inhalation exposure. Additional animal data would be useful in predicting the rate and extent of the inhalation absorption of various silver compounds in humans.

The only information that exists regarding distribution of silver in humans comes from an accidental exposure to an unknown quantity of radiolabeled silver metal dust. The distribution of various silver compounds is known in animals following inhalation and intravenous exposure; only qualitative information exists for oral or dermal exposure. Quantitative data on the distribution of various silver compounds following oral and dermal exposure would be useful when predicting the distribution of silver following exposure to specific silver compounds in humans.

There are data to assess the metabolic fate of silver compounds in humans and animals. Additional studies may shed light on possible variation in susceptibility to silver-related toxic effects. Elucidating the mechanism by which silver exerts toxicity in mammalian cells would assist in evaluating how this affects the health of the whole organism.

The kinetics of the excretion of various silver compounds are well characterized in animals and limited human data exist for inhalation and oral exposure. Further study into (1) the underlying basis for observed species differences; (2) quantitation of the elimination of dermally absorbed silver compounds; and (3) the basis for observed interpersonal differences in tolerance would aid in identification of human subpopulations with varying susceptibilities to the toxic effects of silver.

Comparative Toxicokinetics. A limited number of studies exist regarding the comparative toxicokinetics of orally administered silver compounds in rats, dogs, monkeys, and humans. A more complete comparison of the absorption and elimination of silver in humans and rats may be warranted given that much of the toxicokinetic data comes from rats. It would also be useful to acquire data on the comparative toxicokinetics of various silver compounds in several species of experimental animals and in humans following inhalation and dermal exposure in order to model the kinetics of silver deposition across different exposure scenarios and within sensitive populations.

2.8.3 On-going Studies

No on-going studies were identified that explore the health effects or toxicokinetics of silver or that attempt to associate silver levels in human tissues with effects.