Toxicological Profile for

SILVER

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

TP-90-24

TOXICOLOGICAL PROFILE FOR SILVER

Prepared by:

Clement International Corporation
Under Contract No. 205-88-0608

Prepared for:

Agency for Toxic Substances and Disease Registry
U.S. Public Health Service

December 1990

DISCLAIMER

The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

FOREWORD

The Superfund Amendments and Reauthorization Act of 1986 (Public Law 99-499) extended and amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law (also known as SARA) directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances which are most commonly found at facilities on the CERCLA National Priorities List and which pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The list of the 200 most significant hazardous substances was published in the Federal Register on April 17, 1987 and on October 20, 1988.

Section 110 (3) of SARA directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. Each profile must include the following content:

> (A) An examination, summary, and interpretation of available toxicological information and epidemiologic evaluations on the hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects,
>
> (B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure which present a significant risk to human health of acute, subacute, and chronic health effects, and
>
> (C) Where appropriate, an identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The original guidelines were published in the Federal Register on April 17, 1987. Each profile will be revised and republished as necessary, but no less often than every three years, as required by SARA.

The ATSDR toxicological profile is intended to characterize succinctly the toxicological and health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature that describes a hazardous substance's toxicological properties. Other literature is presented but described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

Each toxicological profile begins with a public health statement, which describes in nontechnical language a substance's relevant toxicological properties. Following the statement is material that presents levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health will be identified by ATSDR, the National Toxicology Program of the Public Health Service, and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the front of the document.

The principal audiences for the toxicological profiles are health professionals at the federal, state, and local levels, interested private sector organizations and groups, and members of the public. We plan to revise these documents in response to public comments and as additional data become available; therefore, we encourage comment that will make the toxicological profile series of the greatest use.

This profile reflects our assessment of all relevant toxicological testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, EPA, the Centers for Disease Control, and the National Toxicology Program. It has also been reviewed by a panel of nongovernment peer reviewers and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

William L. Roper, M.D., M.P.H.
Administrator
Agency for Toxic Substances
and Disease Registry

CONTENTS

FOREWORD iii

LIST OF FIGURES ix

LIST OF TABLES xi

1. PUBLIC HEALTH STATEMENT 1
   1.1 WHAT IS SILVER? 1
   1.2 HOW MIGHT I BE EXPOSED TO SILVER? 2
   1.3 HOW CAN SILVER ENTER AND LEAVE MY BODY? 2
   1.4 HOW CAN SILVER AFFECT MY HEALTH? 3
   1.5 WHAT LEVELS OF EXPOSURE HAVE RESULTED IN HARMFUL HEALTH EFFECTS? 4
   1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO SILVER? 5
   1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH? 5
   1.8 WHERE CAN I GET MORE INFORMATION? 10

2. HEALTH EFFECTS 11
   2.1 INTRODUCTION 11
   2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE 11
      2.2.1 Inhalation Exposure 13
         2.2.1.1 Death 13
         2.2.1.2 Systemic Effects 13
         2.2.1.3 Immunological Effects 16
         2.2.1.4 Neurological Effects 16
         2.2.1.5 Developmental Effects 16
         2.2.1.6 Reproductive Effects 16
         2.2.1.7 Genotoxic Effects 16
         2.2.1.8 Cancer 16
      2.2.2 Oral Exposure 16
         2.2.2.1 Death 16
         2.2.2.2 Systemic Effects 16
         2.2.2.3 Immunological Effects 20
         2.2.2.4 Neurological Effects 20
         2.2.2.5 Developmental Effects 21
         2.2.2.6 Reproductive Effects 21
         2.2.2.7 Genotoxic Effects 21
         2.2.2.8 Cancer 21
      2.2.3 Dermal Exposure 21
         2.2.3.1 Death 21
         2.2.3.2 Systemic Effects 23
         2.2.3.3 Immunological Effects 23
         2.2.3.4 Neurological Effects 23
         2.2.3.5 Developmental Effects 23

2.2.3.6 Reproductive Effects 23
2.2.3.7 Genotoxic Effects 23
2.2.3.8 Cancer 24
2.3 TOXICOKINETICS 24
2.3.1 Absorption 24
2.3.1.1 Inhalation Exposure 24
2.3.1.2 Oral Exposure 25
2.3.1.3 Dermal Exposure 25
2.3.2 Distribution 27
2.3.2.1 Inhalation Exposure 27
2.3.2.2 Oral Exposure 27
2.3.2.3 Dermal Exposure 28
2.3.2.4 Other Routes of Exposure 28
2.3.3 Metabolism 30
2.3.4 Excretion 30
2.3.4.1 Inhalation Exposure 30
2.3.4.2 Oral Exposure 31
2.3.4.3 Dermal Exposure 32
2.3.4.4 Other Routes of Exposure 32
2.4 RELEVANCE TO PUBLIC HEALTH 32
2.5 BIOMARKERS OF EXPOSURE AND EFFECT 38
2.5.1 Biomarkers Used to Identify or Quantify Exposure to Silver 40
2.5.2 Biomarkers Used to Characterize Effects Caused by Silver 41
2.6 INTERACTIONS WITH OTHER CHEMICALS 42
2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE 43
2.8 ADEQUACY OF THE DATABASE 43
2.8.1 Existing Information on Health Effects of Silver 43
2.8.2 Identification of Data Needs 44
2.8.3 On-going Studies 50

3. CHEMICAL AND PHYSICAL INFORMATION 51
3.1 CHEMICAL IDENTITY 51
3.2 PHYSICAL AND CHEMICAL PROPERTIES 51

4. PRODUCTION, IMPORT, USE AND DISPOSAL 65
4.1 PRODUCTION 65
4.2 IMPORT 66
4.3 USE 66
4.4 DISPOSAL 66

5. POTENTIAL FOR HUMAN EXPOSURE 69
5.1 OVERVIEW 69
5.2 RELEASES TO THE ENVIRONMENT 70
5.2.1 Air 70
5.2.2 Water 70
5.2.3 Soil 70
5.3 ENVIRONMENTAL FATE 72
5.3.1 Transport and Partitioning 72
5.3.2 Transformation and Degradation 74

5.3.2.2 Water 74
5.3.2.3 Soil 74
5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT 75
5.4.1 Air 75
5.4.2 Water 75
5.4.3 Soil 76
5.4.4 Other Media 77
5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE 78
5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES 79
5.7 ADEQUACY OF THE DATABASE 80
5.7.1 Identification of Data Needs 80
5.7.2 On-going Studies 82

6. ANALYTICAL METHODS 85
6.1 BIOLOGICAL MATERIALS 85
6.2 ENVIRONMENTAL SAMPLES 91
6.3 ADEQUACY OF THE DATABASE 93
6.3.1 Identification of Data Needs 93
6.3.2 On-Going Studies 94

7. REGULATIONS AND ADVISORIES 95

8. REFERENCES 99

9. GLOSSARY 141

APPENDIX 145

LIST OF FIGURES

2-1 Levels of Significant Exposure to Silver - Oral 18

2-2 Existing Information on Health Effects of Silver 45

5-1 Frequency of Sites with Silver Contamination 71

LIST OF TABLES

1-1	Human Health Effects from Breathing Silver	6
1-2	Animal Health Effects from Breathing Silver	7
1-3	Human Health Effects from Eating or Drinking Silver	8
1-4	Animal Health Effects from Eating or Drinking Silver	9
2-1	Levels of Significant Exposure to Silver - Oral	17
2-2	Levels of Significant Exposure to Silver - Dermal	22
2-3	Interspecies Differences in the Oral Absorption of Silver	26
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	29
2-5	Interspecies Differences in the Clearance of Silver Compounds	33
2-6	Genotoxicity of Silver In Vitro	39
3-1	Chemical Identity of Silver	52
3-2	Chemical Identity of Silver Nitrate	53
3-3	Chemical Identity of Silver (I) Oxide	54
3-4	Chemical Identity of Silver (II) Oxide	55
3-5	Chemical Identity of Silver Sulfide	56
3-6	Chemical Identity of Silver Chloride	57
3-7	Physical and Chemical Properties of Silver	58
3-8	Physical and Chemical Properties of Silver Nitrate	59
3-9	Physical and Chemical Properties of Silver (I) Oxide	60
3-10	Physical and Chemical Properties of Silver (II) Oxide	61
3-11	Physical and Chemical Properties of Silver Sulfide	62
3-12	Physical and Chemical Properties of Silver Chloride	63

6-1 Analytical Methods for Determining Silver in Biological Materials 86

6-2 Analytical Methods for Determining Silver in Environmental Samples 88

7-1 Regulations and Guidelines Applicable to Silver 96

1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about silver and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1177 sites on its National Priorities List (NPL). Silver has been found at 27 of these sites. However, we do not know how many of the 1177 NPL sites have been evaluated for silver. As EPA evaluates more sites, the number of sites at which silver is found may change. The information is important for you because silver may cause harmful health effects and because these sites are potential or actual sources of human exposure to silver.

When a chemical is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment as a chemical emission. This emission, which is also called a release, does not always lead to exposure. You can be exposed to a chemical only when you come into contact with the chemical. You may be exposed to it in the environment by breathing, eating, or drinking substances containing the chemical or from skin contact with it.

If you are exposed to a hazardous substance such as silver, several factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such as age, sex, nutritional status, family traits, life style, and state of health.

1.1 WHAT IS SILVER?

Silver is one of the basic elements that make up our planet. Silver is rare, but occurs naturally in the environment as a soft, "silver" colored metal. Because silver is an element, there are no man-made sources of silver. People make jewelry, silverware, electronic equipment, and dental fillings with silver in its metallic form. It also occurs in powdery white (silver nitrate and silver chloride) or dark-gray to black compounds (silver sulfide and silver oxide). Silver could be found at hazardous waste sites in the form of these compounds mixed with soil and/or water. Therefore, these silver compounds will be the main topic of this profile. Throughout the profile the various silver compounds will at times be referred to simply as silver.

Photographers use silver compounds to make photographs. Photographic materials are the major source of the silver that is released into the environment. Another source is mines that produce silver and other metals.

1. PUBLIC HEALTH STATEMENT

The natural wearing down of silver-bearing rocks and soil by the wind and rain also releases large amounts of silver into the environment.

Silver that is released into the environment may be carried long distances in air and water. Rain washes silver compounds out of many soils so that it eventually moves into the groundwater. Silver is stable and remains in the environment in one form or another until it is taken out again by people. Because silver is an element, it does not break down, but it can change its form by combining with other substances. Over time it may change from the form first released, to metallic silver, and then back to the same or other compounds. The form it is found in depends on environmental conditions. More information on the chemical and physical properties of silver compounds can be found in Chapter 3, on its production, use, and disposal in Chapter 4, and on silver in the environment in Chapters 4 and 5.

1.2 HOW MIGHT I BE EXPOSED TO SILVER?

Most people are exposed daily to very low levels of silver mainly in food and drinking water, and less in air. The silver in these sources is at least partially due to naturally occurring silver in water and soil. Skin contact and breathing in air containing silver compounds also occurs in the workplace. Other sources of exposure include the use of silver in medicines, and in activities such as jewelry-making, soldering, and photography. Exposure from everyday use, such as wearing jewelry or eating with silver-coated flatware, is not expected to result in silver being taken into the body.

Silver levels of less than 0.000001 mg silver per cubic meter of air (mg/m^3), 0.2-2.0 parts silver per billion parts water (ppb) in surface waters, such as lakes and rivers, and 0.20-0.30 parts silver per million parts soil (ppm) in soils are found from naturally occurring sources. Silver compounds are also found in groundwater and at hazardous waste sites throughout the United States. Drinking water supplies in the United States have been found to contain silver levels of up to 80 ppb. Surveys show that one-tenth to one-third of samples taken from drinking water supplies (both groundwater and surface water) contain silver at levels greater than 30 ppb. For more information on exposure to silver see Chapter 5.

1.3 HOW CAN SILVER ENTER AND LEAVE MY BODY?

Silver may enter your body through the mouth, throat, or digestive tract after eating food or drinking water that contains silver, or through your lungs after breathing air containing silver. It can also enter your body through your skin when you put your hands into solutions containing silver compounds, such as those used in photography, or when you come in contact with silver-containing powders. Silver is also known to enter the body when medicines containing it are taken or applied to the skin or gums. Generally, much less silver will enter the body through the skin than through the lungs or stomach.

Because many silver compounds dissolve in water and do not evaporate, the most common way that silver may enter the body of a person near a hazardous waste site is by drinking water that contains silver or eating food grown near the site in soil that contains silver. Silver can also enter the body when soil that has silver in it is eaten. Most of the silver that is eaten or breathed in leaves the body in the feces within about a week. Very little passes through the urine. It is not known how much of the silver that enters the body through the skin leaves the body. Some of the silver that is eaten, inhaled, or passes through the skin may build up in many places in the body. More information on how silver enters and leaves the body can be found in Chapter 2.

1.4 HOW CAN SILVER AFFECT MY HEALTH?

Since at least the early part of this century, doctors have known that silver compounds can cause some areas of the skin and other body tissues to turn gray or blue-gray. Doctors call this condition "argyria." Argyria occurs in people who eat or breathe in silver compounds over a long period (several months to many years). A single exposure to a silver compound may also cause silver to be deposited in the skin and in other parts of the body; however, this is not known to be harmful. It is likely that many exposures to silver are necessary to develop argyria. Once you have argyria it is permanent. However, the condition is thought to be only a "cosmetic" problem. Most doctors and scientists believe that the discoloration of the skin seen in argyria is the most serious health effect of silver.

Exposure to dust containing relatively high levels of silver compounds such as silver nitrate or silver oxide may cause breathing problems, lung and throat irritation and stomach pain. These effects have been seen in workers in chemical manufacturing facilities that make silver nitrate and silver oxide. One man developed severe breathing problems shortly after working with molten silver. Skin contact with silver compounds has been found to cause mild allergic reactions, such as rash, swelling, and inflammation, in some people.

Studies of the health effects of silver in animals commonly use silver nitrate. Doctors and scientists assume that effects seen using silver nitrate in animals will be very similar to effects in humans caused by any silver compound. While this is likely to be true, it is still possible that some silver compounds will be more harmful, or toxic, than silver nitrate.

One animal study suggests that long-term exposure (125 days) to moderately high levels of silver nitrate in drinking water may have a slight effect on the brain because exposed animals were less active than animals drinking water without silver. Another study found that some of the animals that drank water containing moderately high levels of silver for most of their lives (9 months or longer) had hearts that were larger than normal. It is not yet known whether these effects would occur in humans. There have been

suggestions in some occupational studies in humans that silver can cause kidney problems; however, more people exposed to silver need to be studied to find out if silver causes these effects.

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

Silver does have helpful uses. For example, silver nitrate was used for many years as drops in newborns' eyes to prevent blindness caused by gonorrhea, and is also used in salves for burn victims. Some water treatment methods (including water filters) also use a form of silver to kill bacteria. More information on the health effects from exposure to silver is presented in Chapter 2. More information on the helpful uses of silver is presented in Chapter 4.

1.5 WHAT LEVELS OF EXPOSURE HAVE RESULTED IN HARMFUL HEALTH EFFECTS?

Reports of cases of argyria suggest that gram amounts of a silver compound taken in medication in small doses over several months may cause argyria in some humans. People who work in factories that manufacture silver compounds can also breathe in the compounds. In the past, some of these workers have become argyric. However, the level of silver in the air and the length of exposure that caused argyria in these workers is not known. It is also not known what level of silver causes breathing problems, lung and throat irritation, or stomach pain in people.

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

There is very little information about health effects following skin contact with silver compounds. Argyria that covers the entire body is not seen following skin contact with silver compounds, although the skin may change color where it touches the silver. However, many people who have used skin creams containing silver compounds such as silver nitrate and silver sulphadiazine have not reported health problems from the silver in the medicine. In one animal study, a strong solution of silver nitrate (about 41 grams of silver nitrate per liter of water which is equal to 41 parts of

silver nitrate per thousand parts of water) applied to the skin of guinea pigs for 28 days did not cause the animals to die; however, it did cause the guinea pigs to stop gaining weight normally. It is not known if this would happen to people if they were exposed the same way.

Tables 1-1 through 1-4 present the information that is available concerning specific levels of exposure and health effects. The amount of silver that has caused death in rats, and that has caused mice to be less active are shown in Table 1-4.

1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO SILVER?

There are reliable and accurate ways of measuring silver in the body. Silver can be measured in the blood, urine, feces, and body tissues of exposed individuals. Because urine and blood samples are easy to get, these fluids are most often used to find out if a person has been exposed to silver in the last week or so. Silver builds up in the body, and the best way to learn if past exposure has occurred is to look for silver in samples of skin. Tests for silver are not commonly done at a doctor's office because they require special equipment. Although doctors can find out if a person has been exposed to silver by having blood or skin samples examined, they can not tell whether any health effects will occur. Information about tests for measuring silver in the body is in Chapters 2 and 6.

1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government has developed regulations and guidelines to protect people from the possible health effects from long-term exposure to silver in drinking water. The Environmental Protection Agency (EPA) suggests that the level of silver in drinking water not be more than 0.05 milligrams per liter of water (mg/L) (which is equal to 50 parts of silver per billion parts of water or ppb). However, in May, 1989, the EPA announced that this restriction on silver levels in drinking water might be removed. For short-term exposures (1-10 days), EPA suggests that drinking water levels of silver not be more than 1.142 mg/L (which is equal to 1.142 parts of silver per million parts of water or ppm).

Any release to the environment of more than 1 pound silver nitrate or 1000 pounds of silver alone should be reported to the National Response Center. To limit the amount silver workers are exposed to during an 8-hour shift for a 40-hour work week, the Occupational Safety and Health Administration (OSHA) has set a legal limit (Permissible Exposure Limit or PEL) of 0.01 milligrams of silver per cubic meter of air (mg/m^3) in workroom air.

TABLE 1-1. Human Health Effects from Breathing Silver*

Short-term Exposure (less than or equal to 14 days)		
Levels in Air	Length of Exposure	Description of Effects
		The health effects resulting from short-term exposure of humans to air containing specific levels of silver are not known.
Long-term Exposure (greater than 14 days)		
Levels in Air	Length of Exposure	Description of Effects
		The health effects resulting from long-term exposure of humans to air containing specific levels of silver are not known.

*See Section 1.2 for a discussion of exposures encountered in daily life.

TABLE 1-2. Animal Health Effects from Breathing Silver

Short-term Exposure (less than or equal to 14 days)		
Levels in Air	Length of Exposure	Description of Effects
		The health effects resulting from short-term exposure of animals to air containing specific levels of silver are not known.
Long-term Exposure (greater than 14 days)		
Levels in Air	Length of Exposure	Description of Effects
		The health effects resulting from long-term exposure of animals to air containing specific levels of silver are not known.

TABLE 1-3. Human Health Effects from Eating or Drinking Silver*

Short-term Exposure (less than or equal to 14 days)		
Levels in Food	Length of Exposure	Description of Effects
		The health effects resulting from short-term exposure of humans to food containing specific levels of silver are not known.
Levels in Water		The health effects resulting from short-term exposure of humans to water containing specific levels of silver are not known.
Long-term Exposure (greater than 14 days)		
Levels in Food	Length of Exposure	Description of Effects
		The health effects resulting from long-term exposure of humans to food containing specific levels of silver are not known.
Levels in Water		The health effects resulting from long-term exposure of humans to water containing specific levels of silver are not known.

*See Section 1.2 for a discussion of exposures encountered in daily life.

TABLE 1-4. Animal Health Effects from Eating or Drinking Silver

Short-term Exposure (less than or equal to 14 days)		
Levels in Food	Length of Exposure	Description of Effects*
		The health effects resulting from short-term exposure of animals to food containing specific levels of silver are not known.
Levels in Water (ppm)		
2589	2 weeks	Death in rats.

Long-term Exposure (greater than 14 days)		
Levels in Food	Length of Exposure	Description of Effects*
		The health effects resulting from long-term exposure of animals to food containing specific levels of silver are not known.
Levels in Water (ppm)		
95	125 days	Sluggish behavior in mice.
1587	37 weeks	Decreased weight gain in rats.

*These effects are listed at the level at which they were first observed. They may also be seen at higher levels.

For more information on criteria and standards for silver exposure, see Chapter 7.

1.8 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns not covered here, please contact your State Health or Environmental Department or:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road, E-29
Atlanta, Georgia 30333

This agency can also give you information on the location of the nearest occupational and environmental health clinics. Such clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

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.

2. HEALTH EFFECTS

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.

2. HEALTH EFFECTS

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 glucosaminidase), 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 corneal 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 222.2 mg 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 a 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.

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

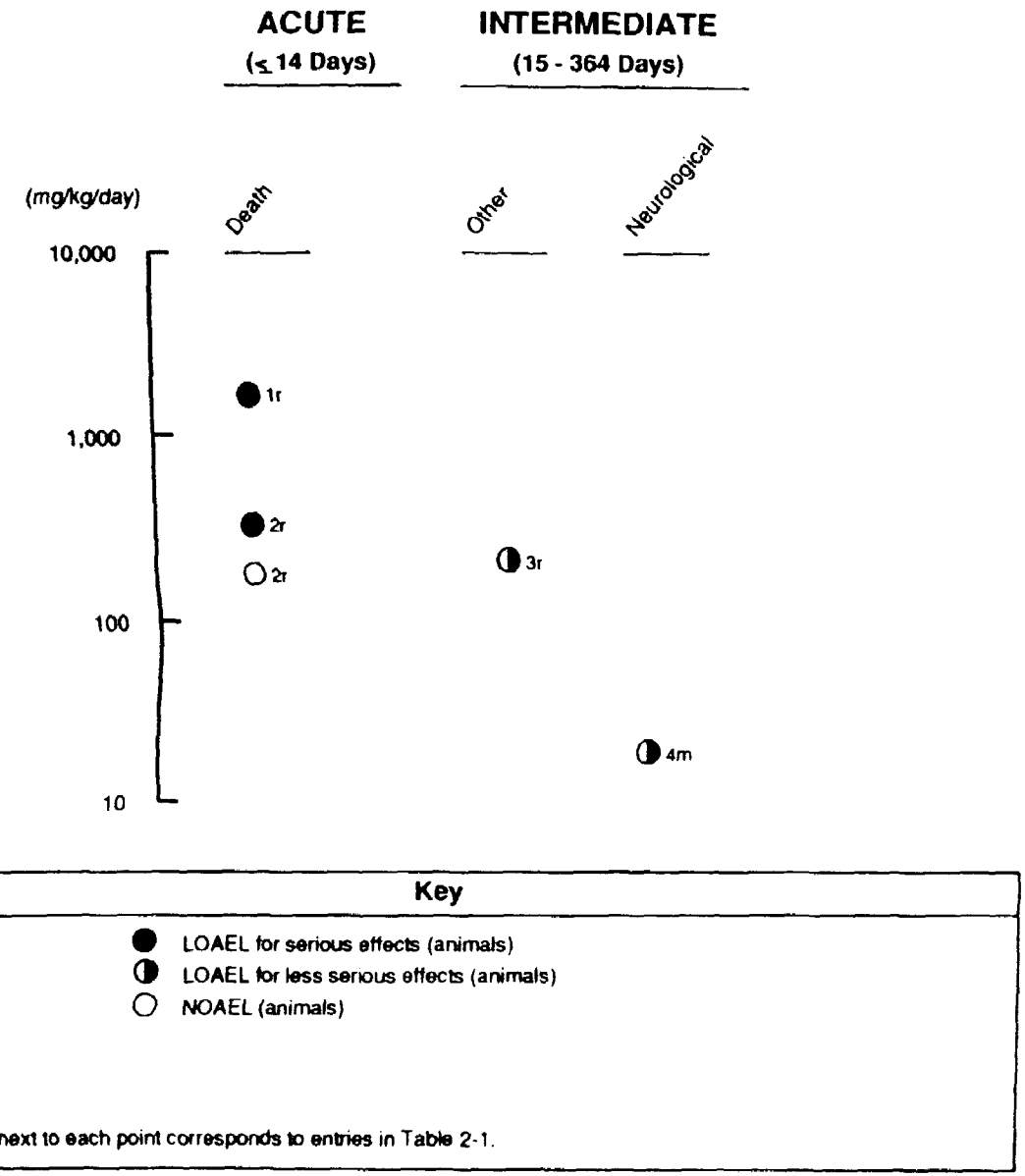

FIGURE 2-1. Levels of Significant Exposure to Silver - Oral

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-dark-gray 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 silver-containing 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 organs", 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 measured 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 2-1 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; Heyl 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

2. HEALTH EFFECTS

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, blue-gray, 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 0-5%) 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 exist, 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/100 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 decreased 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; Heyl 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; Grasso 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 selenium-deficient 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

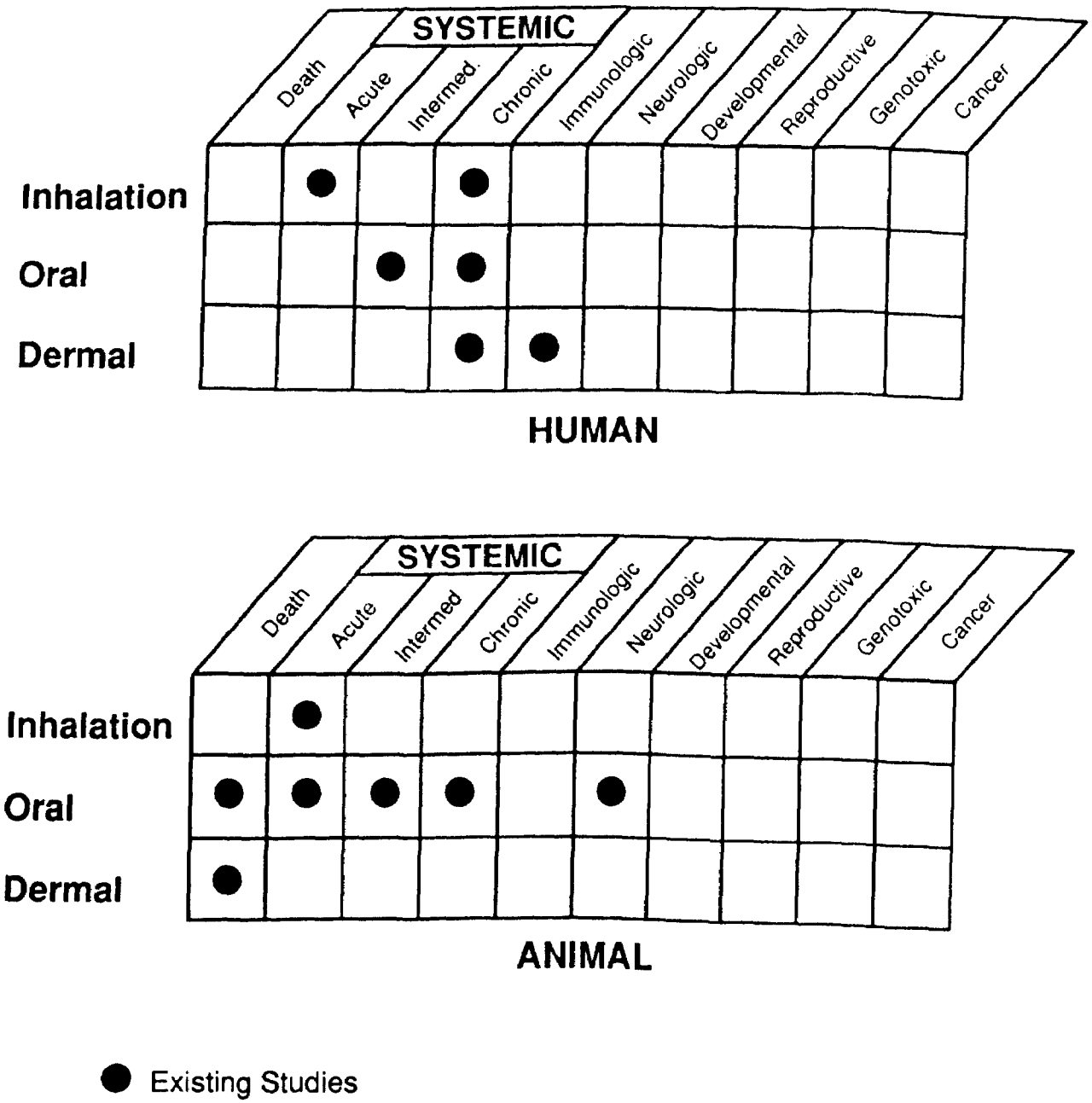

FIGURE 2-2. Existing Information on Health Effects of Silver

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 acute-duration 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. Acute-duration 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. Intermediate-duration 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 90-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. Well-controlled 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.

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

The synonyms and identification numbers for silver and selected silver compounds are listed in Tables 3-1 through 3-6.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Important physical and chemical properties of silver and selected silver compounds are given in Tables 3-7 through 3-12.

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-1. Chemical Identity of Silver

	Value	Reference
Chemical name	Silver	
Synonyms	Silver; argentum; argentum crede; CI 77820; shell silver; silver atom; silver colloidal; silflake; silpowder; silber	CHEMLINE 1988; HSDB 1988
Trade names	No data	
Chemical formula	Ag	Grayson 1983; Windholz 1983
Chemical structure	Ag	HSDB 1988
Wiswesser	• Ag	HSDB 1988
Identification numbers:		
CAS Registry	7440-22-4	HSDB 1988
NIOSH RTECS	VW 3500000	HSDB 1988
EPA Hazardous Waste	D011	HSDB 1988
OHM/TADS	7216881	HSDB 1988
DOT/UN/NA/IMCO shipping	No data	
HSDB	5034	HSDB 1988
NCI	No data	
STCC	No data	

HSDB = Hazardous Substance Data Bank; CAS = Chemical Abstracts Services; NIOSH = National Institute for Occupational Safety and Health; RTECS = Registry of Toxic Effects of Chemical Substances; EPA = Environmental Protection Agency; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; NCI = National Cancer Institute; and STCC = Standard Transport Commodity Code.

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-2. Chemical Identity of Silver Nitrate

	Value	Reference
Chemical name	Silver nitrate	
Synonyms	Lunar caustic; fused silver nitrate; molded silver nitrate; argenti; nitras; nitric acid silver (I) salt; nitric acid silver (1+) salt; Silver (1+) nitrate	HSDB 1988; Weiss 1986; Windholz
Trade names	No data	
Chemical formula	$AgNO_3$	Grayson 1983; Weiss 1986
Chemical structure	$Ag^+ \ NO_3^-$	HSDB 1988
Wiswesser	AG N-03	HSDB 1988
Identification numbers:		
CAS Registry	7761-88-8	Grayson 1983; Weiss 1986
NIOSH RTECS	VW 4725000	HSDB 1988
EPA Hazardous Waste	No data	
OHM/TADS	7216883	HSDB 1988
DOT/UN/NA/IMCO shipping	DOT 1493	Weiss 1986
	UN 1493	HSDB 1988
	IMCO 5.1	
HSDB	685	HSDB 1988
NCI	No data	
STCC	49 187 42	HSDB 1988

HSDB = Hazardous Substance Data Bank; CAS = Chemical Abstracts Services; NIOSH = National Institute for Occupational Safety and Health; RTECS = Registry of Toxic Effects of Chemical Substances; EPA = Environmental Protection Agency; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; NCI = National Cancer Institute; and STCC = Standard Transport Commodity Code.

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-3. Chemical Identity of Silver (I) Oxide

	Value	Reference
Chemical name	Silver (I) oxide	
Synonyms	Argentous oxide; silver (1+) oxide; disilver oxide; silver oxide	Windholz 1983
Trade names	No data	
Chemical formula	Ag_2O	Grayson 1983; Weiss 1986
Chemical structure	Ag^+ O^{2-} Ag^+	RTECS 1989
Wiswesser	AG 2-0	RTECS 1989
Identification numbers:		
CAS Registry	20667-12-3	Grayson 1983
NIOSH RTECS	VW 4900000	RTECS 1989
EPA Hazardous Waste	No data	
OHM/TADS	No data	
DOT/UN/NA/IMCO shipping	IMO/UN-not listed	Weiss 1986
HSDB	No data	
NCI	No data	
STCC	No data	

RTECS = Registry of Toxic Effects of Chemical Substances; CAS = Chemical Abstracts Services; NIOSH = National Institute for Occupational Safety and Health; EPA = Environmental Protection Agency; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; HSDB = Hazardous Substance Data Bank; NCI = National Cancer Institute; and STCC = Standard Transport Commodity Code.

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-4. Chemical Identity of Silver (II) Oxide

	Value	Reference
Chemical name	Silver (II) oxide	
Synonyms	Argentic oxide; silver peroxide; silver suboxide; divasil	Windholz 1983
Trade names	No data	
Chemical formula	AgO	Grayson 1983
Chemical structure	Ag^{2+} O^{2-}	Grayson 1983
Wiswesser	No data	
Identification numbers:		
CAS Registry	1301-96-8, 35366-11-1	Grayson 1983
NIOSH RTECS	No data	
EPA Hazardous Waste	No data	
OHM/TADS	No data	
DOT/UN/NA/IMCO shipping	No data	
HSDB	No data	
NCI	No data	
STCC	No data	

CAS = Chemical Abstracts Services; NIOSH = National Institute for Occupational Safety and Health; RTECS = Registry of Toxic Effects and Chemical Registry; EPA = Environmental Protection Agency; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; HSDB = Hazardous Substance Data Bank; NCI = National Cancer Institute; and STCC = Standard Transport Commodity Code.

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-5. Chemical Identity of Silver Sulfide

	Value	Reference
Chemical name	Silver sulfide	
Synonyms	Acanthite; argentous sulfide	Weast 1988 Windholz 1983
Trade names	No data	
Chemical formula	Ag_2S	Grayson 1983
Chemical structure	Ag^+ S^{2-} Ag^+	Windholz 1983
Wiswesser	No data	
Identification numbers:		
CAS Registry	21548-73-2	Grayson 1983
NIOSH RTECS	No data	
EPA Hazardous Waste	No data	
OHM/TADS	No data	
DOT/UN/NA/IMCO shipping	*No data*	
HSDB	No data	
NCI	No data	
STCC	No data	

CAS = Chemical Abstracts Services; NIOSH = National Institute for Occupational Safety and Health; RTECS = Registry of Toxic Effects of Chemical Substances; EPA = Environmental Protection Agency; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; and STCC = Standard Transport Commodity Code.

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-6. Chemical Identity of Silver Chloride

	Value	Reference
Chemical name	Silver chloride	
Synonyms	Silver (I) chloride; Silver monochloride	RTECS 1988
Trade names	No data	
Chemical formula	AgCl	Grayson 1983
Chemical structure	Ag^+ Cl^-	RTECS 1988
Wiswesser	No data	
Identification numbers:		
CAS Registry	7783-90-6	Grayson 1983
NIOSH RTECS	VW 3563000	RTECS 1988
EPA Hazardous Waste	No data	
OHM/TADS	No data	
DOT/UN/NA/IMCO shipping	No data	
HSDB	No data	
NCI	No data	
STCC	No data	

RTECS = Registry of Toxic Effects of Chemical Substances; CAS = Chemical Abstracts Services; NIOSH = National Institute for Occupational Safety and Health; EPA = Environmental Protection Agency; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; HSDB = Hazardous Substance Data Bank; NCI = National Cancer Institute; and STCC = Standard Transport Commodity Code.

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-7. Physical and Chemical Properties of Silver

	Value	Reference
Molecular weight	107.868	Weast 1988
Color	Lustrous, white	Weast 1988
Physical state	Solid metal	Grayson 1983
Valence state	+1,+2	Windholz 1983
Melting point	961.93°C	Weast 1988
Boiling point	2,212°C at 760 mmHg	Weast 1988
Density at 20°C	10.50 g/cm^3	Weast 1988
20°C	10.43 g/cm^3 (hard drawn)	Grayson 1983
20°C	10.49 g/cm^3 (annealed	Grayson 1983
Odor	No data	
Odor threshold:		
Water	No data	
Air	No data	
Solubility:		
Water at 20°C	Insoluble; soluble in nitric acid, not in sulfuric acid and alkali cyanide solutions	Windholz 1983; ITII 1982
Organic solvents	No data	
Partition coefficients	No data	
Vapor pressure:		
Liquid silver at 1,865°C	100 mmHg	Weast 1988
Henry's law constant	No data	
Autoignition temperature	No data	
Flashpoint	No data	
Flammability limits	Dust is moderately flammable	ITII 1982
Conversion factors	Troy ounces x 31.1034768 = grams	Weast 1988

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-8. Physical and Chemical Properties of Silver Nitrate

	Value	Reference
Molecular weight	169.89	Weast 1988
Color	Colorless or white	Grayson 1983
Physical state	Solid crystalline	Weast 1988
Melting point	212°C	Grayson 1983
Boiling point	Decomposes at 440°C	Grayson 1983
Density at 19°C	4.35	HSDB 1988
at 19°C	4.33	Weiss 1986
Odor	Odorless	Weiss 1986
Odor threshold:		
Water	No data	
Air	No data	
Solubility:		
Water at 0°C	122 g/100 mL H_2O at 0°C	HSDB 1988
Organic solvents	Soluble in ethanol and acetone	Grayson 1983
Partition coefficients	No data	
Vapor pressure	No data	
Henry's law constant	No data	
Autoignition temperature	Not flammable	Weiss 1986
Flashpoint	Not flammable	Weiss 1986
Flammability limits	Not flammable	Weiss 1986

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-9. Physical and Chemical Properties of Silver (I) Oxide

	Value	Reference
Molecular weight	231.8	Weiss 1986
Color	Dark brown-to-black	Windholz 1983
Physical state	Solid crystalline	Weast 1988; Weiss 1986; Windholz 1983
Melting point	Decomposes at 230°C	Weast 1988
Boiling point	*Decomposes between 200°-300°C*	*Windholz 1983*
	Decomposition complete at 300°C	Grayson 1983
Density at 20°C	7.14 g/cm^3	Weiss 1986
Odor	Odorless	Weiss 1986
Odor threshold:		
Water	No data	
Air	No data	
Solubility:		
Water at 25°C	$2.2x10^{-2}$ g/L	Grayson 1983
Organic solvents	Practically insoluble in alcohol	Windholz 1983
Partition coefficients	No data	
Vapor pressure	No data	
Henry's law constant	No data	
Autoignition temperature	*No data*	
Flashpoint	Not flammable	Weiss 1986
Flammability limits	Not flammable	Weiss 1986

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-10. Physical and Chemical Properties of Silver (II) Oxide

	Value	Reference
Molecular weight	123.88	Windholz 1983
Color	Charcoal gray powder, black crystal	Grayson 1983; Windholz 1983
Physical state	Solid	Windholz 1983
Melting point	No data	
Boiling point	Decomposes above 100°C	Windholz 1983
Density	No data	
Odor	No data	
Odor threshold:		
Water	No data	
Air	No data	
Solubility:		
Water at 20°C	Decomposes in aqueous solution	Windholz 1983
Organic solvents	No data	
Partition coefficients:	No data	
Vapor pressure	No data	
Henry's law constant	No data	
Autoignition temperature	No data	
Flashpoint	No data	
Flammability limits	No data	

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-11. Physical and Chemical Properties of Silver Sulfide

	Value	Reference
Molecular weight	247.80	Weast 1988
Color	Gray-black	Weast 1988
Physical state	Solid	Grayson 1983
Melting point	No data	
Boiling point	Decomposes at 810°C	Grayson 1983
Density at 20°C	7.326 g/cm^3	Weast 1988
Odor	No data	
Odor threshold:		
Water	No data	
Air	No data	
Solubility:		
Water at 20°C	$1.4x10^{-4}$ g/L	Grayson 1983
Organic solvents	No data	
Partition coefficients	No data	
Vapor pressure	No data	
Henry's law constant	No data	
Autoignition temperature	No data	
Flashpoint	No data	
Flammability limits	No data	

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-12. Physical and Chemical Properties of Silver Chloride

	Value	Reference
Molecular weight	143.34	Windholz 1983
Color	White	Windholz 1983
Physical state	Solid	Windholz 1983
Melting point	455°C	Windholz 1983
Boiling point	1,550°C	Windholz 1983
Density at 20°C	5.56 g/cm^3	Windholz 1983
Odor	No data	
Odor threshold:		
Water	No data	
Air	No data	
Solubility:		
Water at 25°C	1.93 mg/L	Windholz 1983
Organic solvents	No data	
Partition coefficients	No data	
Vapor pressure		
Henry's law constant	No data	
Autoignition temperature	No data	
Flashpoint	No data	
Flammability limits	No data	

4. PRODUCTION, IMPORT, USE AND DISPOSAL

4.1 PRODUCTION

Silver is a rare, but naturally occurring, element. It is often found deposited as a mineral ore in association with other elements. It is acquired primarily as a by-product during the retrieval of copper, lead, zinc, and gold ores (Grayson 1983). The primary silver mines of the United States are located in the Coeur d'Alene mining district in the northern Idaho panhandle (Smith and Carson 1977). This area accounts for approximately 71% of domestic mine production (Drake 1980). It is mined using either open pit or underground methods, and the ore is then upgraded through a series of processes including flotation and smelting. The silver is finally extracted electrolytically by the Moebius process, the Balbach-Thum process, or the Parkers process (Grayson 1983; Smith and Carson 1977).

World mine production in 1986 was 419.8 million troy ounces (for conversion: troy ounces x 31.1034768 = grams) (Reese 1986). Mine production in the United States declined from 1978 to 1986, reaching a low of 34.2 million troy ounces in 1986, due to a combination of falling silver prices and rising production costs (Reese 1986). This trend appeared to continue according to a survey conducted by The Silver Institute in 1988 and 1989. The United States production of silver from ores and concentrates was 3.4 and 4.2 million troy ounces in 1988 and 1989, respectively. However, when recovered silver is included in the production figures, total production was 8.8 and 9.3 million troy ounces for 1988 and 1989, respectively (The Silver Institute 1990). United States consumption in 1986 reached a high of 126.4 million troy ounces, largely due to increased industrial consumption and use in special issue coinage (Reese 1986). In 1987, the estimated consumption was 63.7 million troy ounces for the United States and 172 million troy ounces worldwide (The Silver Institute 1988)

Since 1951, silver consumption has exceeded its extraction from ore. Secondary silver production involves the recovery of silver from new and old scrap, resulting from silver-containing wastes generated by industry and the consumer. Recycled silver accounted for 40% of U.S. refinery production in 1971 and had increased to 67% by 1974 (Smith and Carson 1977). It was estimated to be 61% and 56% in 1988 and 1989, respectively (The Silver Institute 1990). The estimated world-wide recovery of silver from the photographic industry is about 67% of the total used (The Silver Institute 1988). It has been estimated that 80%, 68%, and 75% of today's annual consumption by the electrical, industrial-alloy, and art industries, respectively, is recycled silver, but these estimates may be high.

4.2 IMPORT

The United States 1986 net import reliance approximated 60% of apparent domestic consumption. Despite this, the 1986 U.S. dependence on foreign imports decreased. Import levels fell from 152.6 million troy ounces in 1985 to 144.9 million troy ounces in 1986 (Reese 1986).

The largest decrease in imported silver was from the United Kingdom and Switzerland. For these two countries import levels fell by 18.1 million ounces, primarily in the form of refined bullion. A total of 125.4 million troy ounces of refined silver were imported in 1986 with only 9.5 million troy ounces accounted for in other forms.

U.S. exports of silver decreased slightly from 28.8 million troy ounces in 1985 to 25.1 million troy ounces in 1986 (Reese 1986).

4.3 USE

Silver metal and silver compounds have been and still are used in a wide variety of ways. In the past, silver was used for surgical prostheses and/or splints, fungicides (both of which are now obsolete), and coinage (discontinued from general circulation within the United States in 1970). Although silver still serves some of the above functions, the current uses are even more varied. Photographic materials accounted for 45% of the U.S. consumption in 1986. Electrical and electronic products, such as electrical contacts, silver paints, and batteries, consumed approximately 25%. Silver has been an important component in the manufacture of bearings in the past, although today its use in this area is limited by cost and availability. Silver is also an important component in brazing alloys and solders, which represent approximately 5% of the 1986 silver consumption. More aesthetic uses of silver include electroplated ware, sterling ware, and jewelry; in 1986, they accounted for 11% of recorded uses.

Other uses account for the remaining 14%; these include use in mirrors, dental amalgam, and medical supplies for treatment of burns, use as a catalyst in the manufacture of formaldehyde and ethylene oxide, as an active agent for purification and disinfection of drinking water and water in swimming pools, in certain chemical analyses involving titration, and in cloud seeding (Grayson 1983; HSDB 1988; NRC 1977; Smith and Carson 1977). Silver ions are also used medically as an antibacterial agent (Becker 1987; Becker et al. 1978; Fox et al. 1969; Webster et al. 1981).

4.4 DISPOSAL

Treatment of air emissions containing silver is not a concern as atmospheric emissions rarely approach the federal threshold limit value for occupational exposure of 0.01 mg/m^3 (Smith and Carson 1977).

Moreover, as consumption of silver-containing products outweighs supply, these products tend to be recycled whenever feasible. The largest source of nonrecycled silver in the waste stream is attributable to photographic material use by small-scale consumers (Smith and Carson 1977). This tends to be released in the form of silver thiosulfate, which is converted into insoluble silver forms by micro-organisms during wastewater treatment (Grayson 1983). Several methods have been suggested for recovering silver from various waste media, including waste water, solid waste, and gas effluents. These include electrolytic recovery, agglomeration, and metal concentration (CHMR 1989). At present the criteria for land disposal practices are undergoing significant revision, and consultation with environmental regulatory agencies is advised (HSDB 1988).

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Silver is a rare element, which occurs naturally in its pure form as a white, ductile metal, and in ores. It has an average abundance of about 0.1 ppm in the earth's crust and about 0.3 ppm in soils. There are four oxidation states (0, 1+, 2+, and 3+); the 0 and 1+ forms are much more common than the 2+ and 3+ forms. Silver occurs primarily as sulfides, in association with iron (pyrite), lead (galena), and tellurides, and with gold. Silver is found in surface waters in various forms: (1) as the monovalent ion (e.g., sulphide, bicarbonate, or sulfate salts); (2) as part of more complex ions with chlorides and sulfates; and (3) adsorbed onto particulate matter.

Silver is released to air and water through natural processes such as the weathering of rocks and the erosion of soils. Important sources of atmospheric silver from human activities include the processing of ores, steel refining, cement manufacture, fossil fuel combustion, municipal waste incineration, and cloud seeding. The total U.S. annual release of silver to the environment as a result of human activities in 1978 was estimated to be approximately 2 million kg. Of this amount, 77% was from land disposal of solid waste, 17% was discharged to surface waters, and 6% emitted to the atmosphere. Ore smelting and fossil fuel combustion emit fine particles of silver that may be transported long distances and deposited with precipitation. The major source of release to surface waters is effluent from photographic processing. Releases from the photographic industry and from disposal of sewage sludge and refuse are the major sources of soil contamination with silver. Sorption is the dominant process controlling partitioning in water and movement in soil. Silver may leach from soil into groundwater; acidic conditions and good drainage increase the leaching rate. Silver is bioconcentrated to a moderate extent in fish and invertebrates.

The general population is exposed to silver primarily through the ingestion of drinking water and food. The most recent estimate by NIOSH indicates that about 70,000 people are potentially exposed to silver in workplace environments in the United States. Inhalation is probably the most important route of occupational exposure. Populations with exposure to higher than background levels of silver include workers in industries processing or using the compound and members of the general public who consume drinking water or food containing elevated levels of silver. Sources of elevated dietary silver include seafood from areas near sewage outfalls or industrial sources and crops grown in areas with high ambient levels of silver in the air or soil.

According to the VIEW Database (1989), silver has been found at 27 sites on the National Priority List of 1,177 sites. The frequency of these sites

within the United States can be seen in Figure 5-1. EPA's Contract Laboratory Program (CLP) statistical database indicates that silver has been detected at 100% of the 2,783 Superfund hazardous waste sites that have had samples of all media analyzed by the CLP (CLP 1988).

5.2 RELEASES TO THE ENVIRONMENT

5.2.1 Air

The total U.S. annual anthropogenic release of silver to the atmosphere from production processes and consumptive uses in 1978 was estimated at 77,700 kg (Scow et al. 1981). Of this amount, an estimated 30,000 kg were released from metals production, 22,000 kg from use in electrical contacts and conductors, 9,000 kg from coal and petroleum combustion, 7,000 kg from iron and steel production, 2,000 kg from cement manufacture, and the remainder from miscellaneous uses. Urban refuse was the source of an additional 10,000 kg. Smith and Carson (1977) estimated that cloud seeding with silver iodide contributed 3,100 kg annually (based on data from the early 1970s).

5.2.2 Water

The total U.S. annual release of silver to surface waters in 1978 from production processes and consumptive uses was estimated to be 125,000 kg (Scow et al. 1981). Of this amount, an estimated 65,000 kg were released from photographic developing, 54,000 kg from photographic manufacture, 5,000 kg from metals production, and the remainder from miscellaneous uses. An additional 70,000 kg were estimated to be released from sewage treatment plants, 72,000 kg from urban runoff, and 438,000 kg from natural sources (e.g., soil erosion). Silver released in precipitation as a result of cloud seeding has decreased and is not expected to contribute significant amounts to water (Scow et al. 1981). Leachates containing silver may enter ground waters when tailing ponds or piles are situated in areas with high water tables or when abandoned mines or sections of mines are saturated (Letkiewicz et al. 1984).

Other sources of silver release to surface waters include textile plant wastewater effluent (Rawlings and Samfield 1979); petroleum refinery effluents (Snider and Manning 1982); and quench water and fly ash scrubber water effluents from municipal incinerators (Law and Gordon 1979). Silver was detected in 7 of 58 (12%) samples from the National Urban Runoff Program survey (Cole et al. 1984).

5.2.3 Soil

The total U.S. annual release of silver to land from production processes and consumptive uses in 1978 was estimated at 1.01 million kg (Scow et al. 1981). Of this amount, an estimated 630,000 kg were released from the photographic industry (in manufacture and developing), 165,000 kg from metals

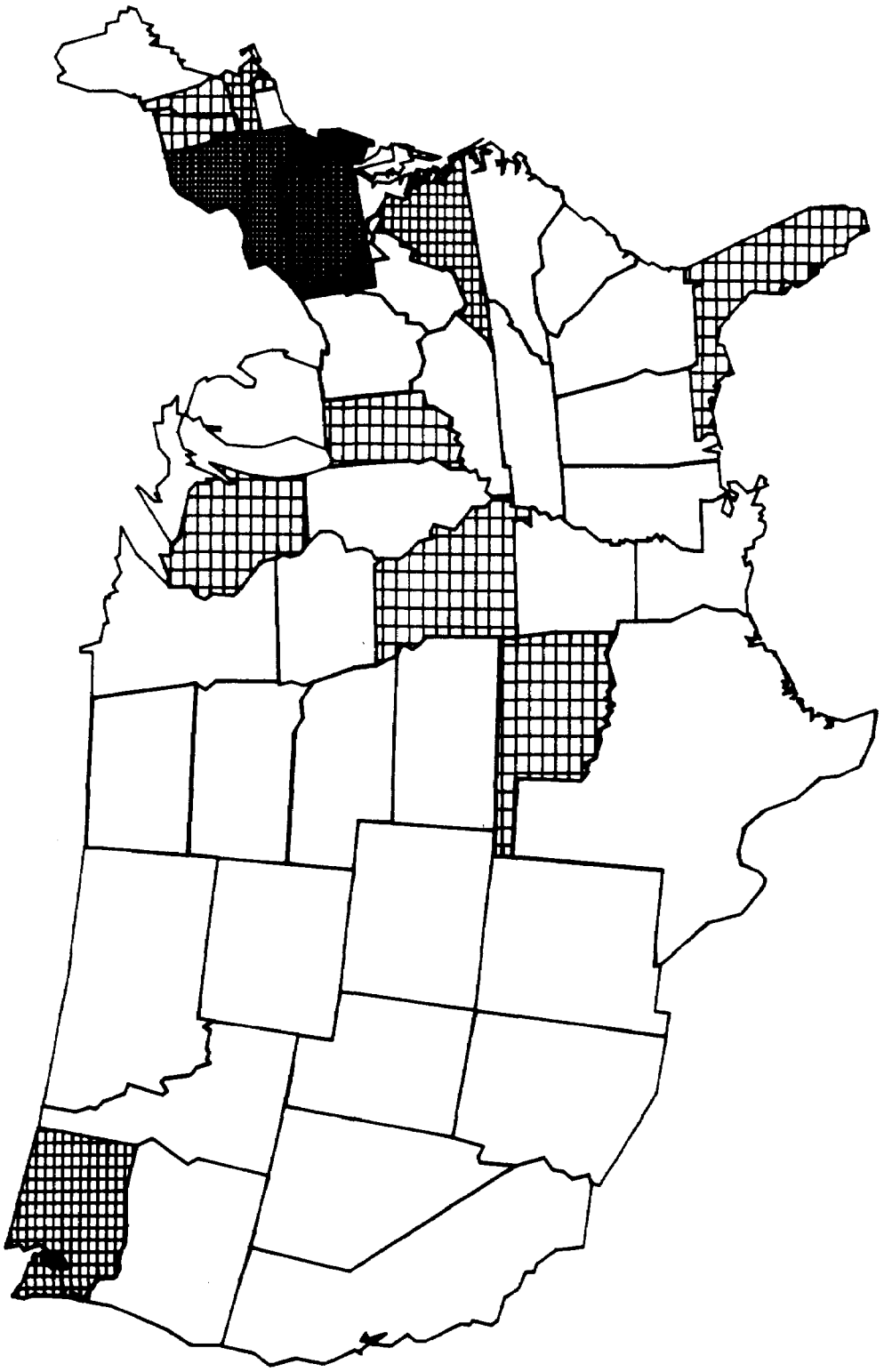

FIGURE 5-1. FREQUENCY OF SITES WITH SILVER CONTAMINATION

production, 150,000 kg from uses in electrical contacts and conductors, 60,000 kg from uses in brazing alloys and solders, and the remainder from miscellaneous uses. An additional 370,000 to 520,000 kg were estimated to be released from urban refuse and 220,000 kg from sewage treatment. Smith and Carson (1977) estimated that the use of silver containing photographic materials contributed an annual 370,000 kg in sewage sludge; of this amount an estimated 52.5% was placed in landfills, 26.7% was lagooned, and 20.8% was spread on land.

The major source of elevated silver levels in cultivated soils is from the application of sewage sludge and sludge effluents as agricultural amendments. Additional anthropogenic sources of silver in soil include atmospheric deposition (especially from ore processing); landfilling of household refuse, sewage sludge, or industrial wastes; and leaching of metal tailings (Smith and Carson 1977).

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

The global biogeochemical movements of silver are characterized by releases to the atmosphere, water, and land by natural and man-made sources, possible long-range transport of fine particles in the atmosphere, wet and dry deposition, and sorption to soil and sediments. The major forms of silver in the atmosphere are probably metallic silver, silver sulfide, silver sulfate, silver carbonate, and silver halides (Smith and Carson 1977). Silver is released to the atmosphere as an aerosol (suspension of solid or liquid particles in a gas such as air). Mining operations such as grinding emit large particles (more than 20 μ diameter) that settle near the source while particles emitted from smelting, fossil-fuel fired power plants, and solid waste incinerators are smaller and are likely to be transported away from the source of release (Scow et al. 1981). Fine particles (less than 20 μ diameter) in the aerosol tend to be transported long distances in the atmosphere and are deposited with precipitation. Long-range atmospheric transport of silver is indicated by several studies in which atmospheric particulate concentrations were elevated above background levels in areas removed from cloud seeding or mining activities (Davidson et al. 1985; Struempler 1975). Scow et al. (1981) estimated that about 50% of the silver released into the atmosphere from industrial operations will be transported more than 100 km and will eventually be deposited by precipitation.

The transport and partitioning of silver in surface waters and soils is influenced by the particular form of the compound. Lindsay and Sadiq (1979) stated that under oxidizing conditions the primary silver compounds would be bromides, chlorides, and iodides, while under reducing conditions the free metal and silver sulfide would predominate. In water, the major forms of silver are as the monovalent ion in the form of sulfate, bicarbonate, or sulfate salts; as part of more complex ions with chlorides and sulfates; and

as an integral part of, or adsorbed onto, particulate matter (Boyle 1968). In one study, silver in river water was primarily found in the following forms: silver ion (Ag^+) -- 53-71%, silver chloride ($AgCl^\circ$) -- 28-45%, silver chloride ion ($AgCl_2^-$) -- 0.6-2.0% (Whitlow and Rice 1985). Callahan et al. (1979) stated that sorption is the dominant process leading to the partitioning of silver in sediments. Significant quantities of silver in water are sorbed by manganese dioxide; pH and oxidation-reduction conditions affect sorption (Anderson et al. 1973). Kharkar et al. (1968) reported that approximately 90% of the silver in rivers was in a dissolved form and 10% was a suspended solid. Concentrations in lake sediments were reported to be 1000 times that of the overlying waters; the highest content was associated with fine-grained sediments (Freeman 1977).

The mobility of silver in soils is affected by drainage (silver tends to be removed from well-drained soils); oxidation-reduction potential and pH conditions (which determine the reactivity of iron and manganese complexes which tend to immobilize silver); and the presence of organic matter (which complexes with silver and reduces its mobility) (Boyle 1968). The distribution coefficient (Kd: ratio of the concentration in soil to the concentration in water) for silver in a number of soils ranged from 10 to 1,000 (Baes and Sharp 1983). Factors that affect the Kd include soil pH, clay content and particle size distribution, organic matter content, and free iron and manganese oxide content. The enhanced ability of organic matter to immobilize silver is demonstrated by the increased levels of silver found in peat and bog soils and in marshes (Boyle 1968). In pasture plants growing in the vicinity of an airborne source of silver such as a smelter, silver in the leaves is apparently derived from deposition of airborne silver, while concentrations in the roots are from soil uptake (Ward et al. 1979). Silver levels in the leaves were slightly greater than levels in the roots.

Silver accumulation in marine algae appears to result from adsorption rather than uptake; bioconcentration factors of 13,000-66,000 have been reported (Fisher et al. 1984).

Data on the potential for accumulation of silver has been studied in several aquatic species. Several of these studies do not conform to current bioconcentration test procedures in terms of numbers of fish, duration of exposure, and measurement of concentrations in aquaria. EPA (1980a) reported a bioconcentration factor of less than 1 in bluegills (Lepomis macrochirus) exposed to silver nitrate for 28 days. Approximate bioaccumulation factors of 4-6 for bluegill were calculated based on a 6-month study and 2-10 for large mouth bass (Micropterus salmoides) exposed to silver nitrate for 4 months (both dry weight) (Coleman and Cearley 1974).

Terhaar et al. (1977) studied bioconcentration (uptake from water) and bioaccumulation (uptake from food and water) of silver thiosulfate complexes in algae (Scenedesmus sp.), water flea (Daphnia magna), mussels (Ligumia sp. and Margaritifera sp.), and fathead minnow (Pimephales promelas) in 10-week

exposures. Bioconcentration indices were 96-150 for algae, 12.2-26 for Daphnia, 5.9-8.5 for mussels, and 1.8-28 for fish. Bioaccumulation indices were 9-26 for Daphnia, 6.6-9.8 for mussels, and 4.0-6.2 for fish. These indices, which are based on measured wet weight concentrations in biota and nominal concentrations in water, indicate little potential for silver biomagnification (systematic increase in residue concentrations moving up a food chain) in the tested aquatic food chain.

Bioconcentration factors of 1,055-7,650 (wet weight) were estimated in a 21-month study with the mussel (Mytilus edulis) in salt water (Calabrese et al. 1984). The clam, Macoma balthica, contained silver at 32-133 μg/g (dry weight tissue) in an area of San Francisco Bay near a sewage outfall; background concentrations in this species in the bay were less than 1 μg/g (Thomson et al. 1984). These data indicate that inputs of silver to an estuary are available to sediment-dwelling animals. Silver from sewage sludge at an ocean disposal site was bioaccumulated by the sea scallop (Placopecten magellanicus). Maximum concentrations in scallops located near the disposal site were 9.08 ppm (dry weight tissue) while scallops located away from the site had levels less than 1 ppm (Pesch et al. 1977). The estimated biological half-lives for the elimination of silver were 26.4 days for the Pacific oyster (Crassostrea gigas) and 149.1 days for the American oyster (C. virginica) (Okazaki and Panietz 1981).

5.3.2 Transformation and Degradation

5.3.2.1 Air

Particulates of metallic silver emitted from the burning of fossil fuels and municipal refuse are likely to become coated with silver oxide, silver sulfide, and silver carbonate as the particles cool and undergo deposition (Smith and Carson 1977).

5.3.2.2 Water

In fresh water, silver may form complex ions with chlorides, ammonium (in areas of maximum biological activity), and sulfates; form soluble organic compounds such as the acetate and the tartrate; become adsorbed onto humic complexes and suspended particulates; and become incorporated into, or adsorbed onto, aquatic biota (Boyle 1968). Where decaying animal and plant material are abundant, silver strongly precipitates as the sulfide or combines with humic materials (Smith and Carson 1977).

5.3.2.3 Soil

Silver tends to form complexes with inorganic chemicals and humic substances in soils (Boyle 1968). Since silver is toxic to soil microorganisms and inhibits bacterial enzymes (Domsch 1984), biotransformation is not expected to be a significant process.

5. POTENTIAL FOR HUMAN EXPOSURE

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

Silver was measured in particulate samples from rural and urban areas both adjacent to and removed from activities such as metal smelting, refining, and silver iodide cloud seeding. Background levels appear to be less than 1 ng/m^3 as evidenced by the measurement of average silver concentrations of 0.018 ng/m^3 at Great Smoky Mountains National Park; 0.012 ng/m^3 at Olympic National Park; and less than 0.19 ng/m^3 at Glacier National Park (Davidson et al. 1975). The highest particulate levels (mean -- 10.5 ng/m^3; range -- 0.936-36.5 ng/m^3) were measured in Kellogg, Idaho (in the Coeur d'Alene River Basin) near a large smelter complex (Ragaini et al. 1977). In an industrialized area of northwest Indiana, silver was measured at less than 1-5 ng/m^3 (Harrison et al. 1971). A level of 1 ng/m^3 was reported by Douglas (1968) in a rural cloud-seeding target area. In a rural area of Nebraska where no cloud seeding was known to have occurred, Struempler (1975) found particulate silver concentrations averaged 0.04-0.15 ng/m^3 during three sampling periods. This researcher theorized that anthropogenic sources, such as long-range transport from cloud seeding, were responsible for the enrichment of silver by factors of 326-355 over its average concentration in the earth's crust. Silver concentrations in precipitation resulting from seeding clouds with silver iodide were 10-4500 ng/L compared with concentrations of 0-20 ng/L without cloud seeding (Cooper and Jolly 1970).

5.4.2 Water

Boyle (1968) reported average (background) ambient concentrations of silver in fresh waters of 0.2 µg/L and in sea water of 0.25 µg/L. Waters that leach silver-bearing deposits (e.g., in mining areas) may carry up to 100 times more silver than other fresh waters (Scow et al. 1981). Leaching is enhanced by low pH (Smith and Carson 1977). In samples of 170 lakes in California, silver concentrations averaged 0.1 µg/L with a maximum of 6.0 µg/L (Bradford et al. 1968). Kharkar et al. (1968) reported that the average silver concentration of 10 U.S. rivers was 0.30 µg/L (range: 0.092-0.55 µg/L). In another survey, Kopp (1969) found silver in 6.6% of 1,577 surface waters sampled with a mean detected concentration of 2.6 µg/L (range: 0.1-38 µg/L). For 1970-1979, according to U.S. surface water sampling data from EPA's STORET database, the annual mean levels ranged from 1 µg/L to 9 µg/L and annual maximum concentrations were 94 µg/L to 790 µg/L (Scow et al. 1981). In 10 out of 13 major U.S. river basins, silver concentrations decreased from 1975-1979 as compared with 1970-1974. Concentrations increased in the North Atlantic, Southeast, and Lower Mississippi basins. In the U.S. Geological Survey, Water Resources Division portion of the database (from the early 1960s to mid-1988), silver was detected in 2,195 of over 10,000 surface water samples; the mean and median concentrations in these samples were 1.9 µg/L and 2.0 µg/L, respectively (Eckel and Jacob 1988).

Hem (1970) reported a median silver concentration of 0.23 μg/L in U.S. drinking water. Letkiewicz et al. (1984) analyzed the results of three surveys of U.S. groundwater and surface water used as drinking water supplies. These surveys were the 1969 U.S. Public Health Service Community Water Supply Survey (CWSS 1969), the 1978 EPA Community Water Supply Survey (CWSS 1978), and the 1978 through 1980 EPA Rural Water Survey (RWS). In CWSS 1969, silver was detected (minimum positive value was 0.1 μg/L) in 309 of 677 groundwater supplies, (mean 1.7 μg/L, median 1.3 μg/L, and range 0.1 to 9 μg/L). Silver was detected in 59 of 109 surface water supplies with a mean and median of 1.3 μg/L and a range of 0.1 to 4 μg/L. In CWSS 1978, silver was detected (minimum positive value was 30 μg/L) in 8 of 81 groundwater supplies (range 30-40 μg/L, mean 31.9 μg/L, and median 30 μg/L). Silver was found in 4 of 25 surface water supplies (range 30-40 μg/L, mean 36.2 μg/L, and median 37.5 μg/L). In the RWS conducted between 1978 and 1980, silver was detected (minimum quantifiable concentration apparently was 20 μg/L) in 10 of 71 groundwater supplies (mean and median 40 μg/L and range 20-80 μg/L). Silver was detected in 8 of 21 surface water supplies. The range, mean, and median of these 8 supplies were 20-60 μg/L, 36.2 μg/L, and 35 μg/L, respectively. Letkiewicz et al. (1984) also summarized information from EPA's Federal Reporting Data System as of 1984, which indicated that 14 public water supplies (13 from groundwater) in the United States reported silver levels above 50 μg/L. Letkiewicz et al. (1984) stated that it is not possible to determine which of these surveys is representative of current levels of silver in the U.S. water supply. The large range in apparent detection limits further limits the usefulness of these data in estimating silver levels in U.S. water supplies.

Silver has been detected with a geometric mean concentration of 6.0 μg/L in groundwater samples from 613 of the 2,783 (22%) hazardous waste sites included in EPA's Contract Laboratory Program (CLP) statistical database (CLP 1988). It has also been detected in surface water samples from 552 of the 2,783 (20%) sites in the CLP statistical database with a geometric mean concentration of 9.0 μg/L (CLP 1988).

5.4.3 Soil

From a series of measurements in Canada, Boyle (1968) estimated that the average silver content of soils (except for mineralized zones such as mining areas) was 0.30 ppm and the average abundance in the earth's crust was 0.10 ppm. The major source of elevated silver levels in cultivated soils is from the application of sewage sludge and sludge effluents (Smith and Carson 1977). The average silver concentration in soils near a lead smelting complex in Kellogg, Idaho (in the Coeur d'Alene River Basin) was 20 ppm (range: 3.2-31 ppm) (Ragaini et al. 1977). Klein (1972) measured soil metal concentrations in the Grand Rapids, Michigan area in order to examine possible relationships between concentrations and land use. Silver concentrations in soils that were classified by land use were 0.13 ppm (residential), 0.19 ppm (agricultural), and 0.37 ppm (industrial) (Klein 1972).

5. POTENTIAL FOR HUMAN EXPOSURE

The Contract Laboratory Program (CLP) statistical database indicates that silver has been detected with a geometric mean concentration of 4.5 ppm in soil samples from 1,807 of 2,783 (65%) hazardous waste sites that have had samples analyzed by the CLP (CLP 1988).

5.4.4 Other Media

Coal has been reported to contain silver at concentrations of up to 10 ppm (Boyle 1968). Klusek et al. (1983) measured the following silver concentrations at a bituminous coal-fired electric generating station: coal - 0.29 mg/kg; fly ash -- 1.6 mg/kg; and bottom ash -- <0.1 mg/kg. In the combustible portions of municipal solid waste, mean silver concentrations were 3 ppm (range: <3-7 ppm) (Law and Gordon 1979). A municipal incinerator was found to emit particles containing 390 ppm silver (Law and Gordon 1979). The mean and maximum silver concentrations in U.S. sewage sludge were 225 mg/kg and 960 mg/kg (dry weight), respectively (Bunch 1982). Sludge silver concentrations (mg/kg dry weight) were reported as follows: from sewage treatment plants with industrial or municipal wastes -- 15-120 mg/kg; from plants with photoprocessing effluents as a source -- 450-27,000 mg/kg (Lytle 1984).

Scow et al. (1981) reported that the median silver concentrations in sewage treatment plant influent and effluent were 0.008 mg/L and 0.002 mg/L, respectively. Treated effluents from a large photographic processing plant contained an average of 0.07 mg/L silver (range: <0.02-0.30 mg/L) in the form of silver thiosulfate complexes, silver bromide, and silver sulfide (Bard et al. 1976).

Cunningham and Stroube (1987) collected samples of various foods in 20 U.S. cities between 1979 and 1980. Silver concentrations (mg/kg wet weight) in composite samples of the following food groups were: dairy products -- <0.061; meat, fish, and poultry -- mean 0.015, range 0-87; cereal and grain products -- mean 0.008, range 0-0.140; leafy vegetables -- mean 0.007, range 0-0.039; fruits -- <0.050; oils and fats -- <0.030. The average silver concentration of a mixture of 201 foods prepared to represent the typical U.S. diet was 0.0091 mg/kg dry weight (Iyengar et al. 1987). The average concentration in cow's milk in the United States has been reported to be 0.047 ppm (range:0.037-0.059 ppm) (Murthy and Rhea 1968). EPA (1980a) summarized data on silver content in food as follows: beef -- 0.004-0.024 mg/kg; pork -- 0.007-0.012 mg/kg; mutton and lamb -- 0.006-0.011 mg/kg; tea -- 0.20-2.00 mg/kg (dry weight); mollusks -- 0.1-10.0 mg/kg.

Mean silver concentrations in one brand of nonfilter and filter cigarettes were reported to be 0.18 mg/kg and 0.27 mg/kg, respectively (Nadkarni et al. 1970).

In a summary of 1975-1979 data on fish tissue from EPA's STORET database, the mean concentration of silver in 221 samples was 0.225 mg/kg (wet weight

total fish), with a range of 0.004-1.900 mg/kg (Scow et al. 1981). In Lake Pontchartrain, Louisiana (which is likely to receive substantial inputs of metals from municipal and agricultural activities) silver concentrations in clams and American oyster tissues were 0.4-2.4 mg/kg and 5.5 mg/kg (all dry weight), respectively (Byrne and DeLeon 1986).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Food and water are the most likely major sources of exposure to natural and anthropogenic silver for the general U.S. population (Letkiewicz et al. 1984). The general population is also exposed through the inhalation of airborne silver and the dental and medical uses of silver. Letkiewicz et al. (1984) estimated that about 50% of the 214 million people in the United States who use public drinking water supplies had silver present in their water at 0.01-10 μg/L; 10-30% may receive water with levels greater than 30 μg/L. They estimated that 46,000 people in the U.S. receive drinking water with silver concentrations exceeding the current U.S. Safe Drinking Water Act maximum contaminant limit of 50 μg/L. Swimming pool water purified with silver-containing systems is another possible source of exposure to silver.

The averaged daily dietary intake (including fluids) of silver has been estimated to be 70 μg/day (Snyder et al. 1975) and 88 μg/day (Kehoe et al. 1940). The average daily dietary intake of two subjects over 30 days was determined to be 35-44 μg/day (Tipton et al. 1966). The silver content of food was estimated at 4.5 μg/day based on the content of a mixture of 201 foods prepared to represent the typical U.S. diet (Iyengar et al. 1987). Most of the U.S. population breathes air containing a maximum of 1.0 ng/m^3 silver, which contributes a maximum of 0.023 μg/day. Drinking water supplies containing 10 μg/L would provide an estimated 20 μg/day of the 70-88 μg/day estimated daily intake. At levels of 30-50 μg/L, drinking water contributes 60-100 μg/day (based on an estimated daily water intake of 2 L) and constitutes the major source of silver intake (Letkiewicz et al. 1984). Although silver has been detected in cigarettes, the average daily intake from smoking has not been determined. A very limited use of silver salts is in purification systems in isolated locations (such as mountain cabins and in space missions) (Silver Institute 1975).

The 1972-1974 National Occupational Hazard Survey (NOHS), conducted by NIOSH estimated that 19,343 workers in 2,163 plants were potentially exposed to silver in 1970 (NIOSH 1976). The largest number of exposed workers were in special trade contracting, primary metal industries, and industries using electrical machinery and electrical equipment and supplies. The occupational groups with the largest number of exposed workers were air conditioning, heating and refrigeration mechanics and repairmen; plumbers and pipefitters; miscellaneous assemblers; welders and flamecutters; and miscellaneous machine operators.

Preliminary data from a second workplace survey, the 1980-1983 National Occupational Exposure Survey (NOES) conducted by NIOSH, indicated that 67,054 workers, including 15,763 women, in 3,123 plants were potentially exposed to silver in the workplace in 1980 (NIOSH 1984a). These estimates were derived from observations of the actual use of silver (67% of total estimate) and the use of trade name products known to contain the compound (33%). The largest number of workers were exposed in the primary metal industries, business services, health services, instruments and related products industries, and fabricated metal products industries.

Neither the NOHS nor the NOES databases contain information on the frequency, concentration, or duration of exposure of workers to any of the chemicals listed therein. These surveys provide only estimates of the number of workers potentially exposed to chemicals in the workplace.

Additional industrial processes which act as potential sources of occupational exposure to silver include the processing of silver chemicals such as silver nitrate and silver oxide for uses such as photography, and smelting and refining of silver-containing ores (DiVincenzo et al. 1985).

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

The most likely sources of higher than background levels of silver for the general population are ingestion of contaminated food and drinking water. The estimated 46,000 persons in the United States whose drinking water contains more than 50 μg/L silver (attributable to natural and/or anthropogenic sources) would have an estimated daily intake of at least 100 μg/day from water alone (Letkiewicz et al. 1984). Higher levels of silver have been detected in shellfish near industrial or sewage inputs (Byrne and DeLeon 1986; Pesch et al. 1977; Thomson et al. 1984) and are likely to occur in crops grown on sludge-amended soils, in the vicinity of smelters or mining operations, or in areas with naturally high background silver levels.

Elevated atmospheric silver concentrations have been attributed to smelting and refining of silver and other metals, and the use of silver iodide in cloud seeding (Scow et al. 1981). Populations living close to mines may have higher exposures. Approximately 71% of domestic mine production occurs in Idaho, Arizona, and Colorado; the Coeur d'Alene River Basin in Idaho supplies the greatest amount of silver (Drake 1980). Crops grown on soils with elevated silver concentrations (either from anthropogenic sources or from naturally high background levels) or exposed to high ambient atmospheric concentrations are likely to become enriched with silver (Ragaini et al. 1977; Ward et al. 1979).

Silver has been used in lozenges and chewing gums designed to aid the cessation of smoking. Silver acetate in chewing gum has been classified as an over-the-counter smoking deterrent by the Food and Drug Administration (Malcolm et al. 1986). Several cases of high body levels of silver have been

reported (Malcolm et al. 1986). A skin silver concentration thousands of times higher than would be expected as a normal value was found in a patient after an estimated 6 month exposure to silver acetate lozenges (East et al. 1980; MacIntyre et al. 1978).

Scow et al. (1981) estimated that a person developing six rolls of film could be exposed to up to 16 grams of silver through dermal contact with photographic solutions. However, many people use implements or wear gloves during film developing and therefore this is not expected to result in widespread, high level exposures. Inhalation was not expected to be a significant route of uptake during film processing because of the low volatility of silver in solution.

5.7 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.

5.7.1 Identification of Data Needs

Physical and Chemical Properties. No data exist on the partition coefficients and Henry's law constant for silver and its compounds. A vapor pressure has been determined for silver at very high temperatures (greater than 900°C), but not for any of its compounds. Generally, the fate of silver in the environment is fairly well understood; however, a determination of these environmentally relevant values for silver compounds might provide a more complete estimation of the fate of silver in the environment. Tables 3-7 to 3-12 contain information on the known physical and chemical properties of silver and several important silver compounds.

Production, Use, Release, and Disposal. The production, use, release, and disposal of silver is well characterized and indicates that risk of exposure for the general population is potentially high. Silver and silver compounds are produced and used for a wide variety of common products and

applications, including photographic materials, jewelry, tooth amalgams, medical supplies, and water purification. The extensive production and use of silver leads to a high risk of release to the environment, particularly to soil and water. Silver has been detected in various food products, with the highest levels detected in fish. Silver is both rare and valuable, and consumption exceeds production. Therefore, manufacturers attempt to conserve the metal by limiting releases and recycling instead of disposing of the metal. Methods exist for recovering silver from several waste media. Improvements in capturing released silver before it reaches the environment would be beneficial for both economic and health reasons.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to EPA. The Toxics Release Inventory (TRI), which contains this information for 1987, became available in May of 1989. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate. The factors governing the environmental fate of silver are not well characterized. While silver and its compounds are transported in the air, water, and soil, and are partitioned between these media, the mechanisms of transport and partitioning are not well-defined. No partition coefficients or constants have been determined for silver or its compounds. Little information was found in the available literature on transformation of silver in water or soil. Some microorganisms present in these media may be able to transform silver and silver compounds; however, silver is not expected to be significantly transformed in the environment because it is toxic to microorganisms. Further information on the size and flux of environmental compartments and the transport and transformations of silver and silver compounds in the environment would be useful in defining pathways for potential human exposure.

Bioavailability from Environmental Media. *Silver is known to be absorbed* from the lungs following inhalation exposure to silver dust or air contaminated with silver compounds, but data on the extent and rate of absorption are limited. Silver is also absorbed following oral or dermal exposure to drinking water, solutions and medical products containing silver compounds. No data were located on bioavailability of silver from soil, plant material, or foods. However, silver is found in all these environmental media and it is likely that some silver might be absorbed from these sources. Further information on the bioavailability of silver from contaminated air, water, soil, plants, and other foods would help in assessing the health risk associated with increased exposures that might occur in populations in the vicinity of hazardous waste sites.

Food Chain Bioaccumulation. The data available indicate that silver can bioconcentrate to a limited extent in algae, mussels, clams, and other aquatic

Food Chain Bioaccumulation. The data available indicate that silver can bioconcentrate to a limited extent in algae, mussels, clams, and other aquatic organisms. However, many of the studies that were performed do not conform to the current state of the art in terms of sample size, duration, and analysis of contaminant levels in aquaria. Reliable data would be useful in determining the possibility of biomagnification and in defining pathways for general population exposure, as well as in estimating exposures from NPL site contamination.

Exposure Levels in Environmental Media. Silver has been detected in all environmental media, but most of the data are not current. Current data from EPA's CLP indicate silver is found at levels above background in ground water, surface water and soil near hazardous waste sites. Elevated levels of silver have been detected in shellfish located near sources of silver pollution. Estimates of average daily human intake from air, drinking water, food, and total diet have been calculated. More current information, that better defines major sources and forms of silver, would increase the accuracy of estimates of daily exposure to silver. This information could be used to develop a more thorough representation of the contribution of silver exposure from contamination at hazardous waste sites. Data that better characterize levels in fish and shellfish would aid in identifying populations with potentially high exposures to silver from these sources.

Exposure Levels in Humans. Silver has been detected in the blood, tissues, urine, and feces of humans. The only biological monitoring studies located consisted of small numbers of worker populations in chemical manufacturing industries. Studies that better characterize important sources of general population exposure and define populations with potentially high exposure, such as those located near hazardous waste sites, would be helpful. More specific information concerning the chemical form of silver present at hazardous waste sites would also be useful. These data would assist in developing a more accurate estimate of the potential for silver exposure from hazardous waste sites contaminated with the metal.

Exposure Registries. No exposure registries for silver were located. This compound is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The compound will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to the exposure to this compound.

5.7.2 On-going Studies

No long-term research studies on the environmental fate of silver were identified. However, environmental monitoring being conducted in conjunction with remedial investigation/feasibility studies at NPL sites where silver has

been found should add useful information regarding environmental concentrations, chemical species, fate, and transport of the compounds.

No on-going studies or long-term research concerning occupational or general population exposures to silver were identified.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting and/or measuring and monitoring silver in environmental media and in biological samples. The intent is not to provide an exhaustive list of analytical methods that could be used to detect and quantify silver. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used to detect silver in environmental samples are the methods approved by federal agencies such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by a trade association such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that refine previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

The analytical methods used to quantify silver in biological and environmental samples are summarized in two tables. Applicable analytical methods for determining silver in biological fluids and tissues are listed in Table 6-1, and those used for determining silver in various environmental samples are listed in Table 6-2.

6.1 BIOLOGICAL MATERIALS

Trace levels (10^{-6} to 10^{-9} g/g of sample) of silver can be accurately determined in biological samples by several different analytical techniques, provided that the analyst is well acquainted with the specific problems associated with the chosen method. These methods include high frequency plasma torch-atomic emission spectroscopy (HFP-AES), neutron activation analysis (NAA), graphite furnace (flameless) atomic absorption spectroscopy (GFAAS), flame atomic absorption spectroscopy (FAAS), and micro-cup atomic absorption spectroscopy (MCAAS).

Atomic absorption spectroscopy equipped with various atomizers is the best and most prevalent analytical method used to analyze trace amounts of silver in biological tissues and fluids. GFAAS offers high detectability (subnanogram/gram of sample) and requires relatively small samples for analysis of biological tissues (DiVincenzo et al. 1985; Segar and Gilio 1973). Background absorption from sample matrix components can be a problem, but correction using a deuterium continuum light source is adequate if cautiously applied (Segar and Gilio 1973). The detection limit of silver in biological tissues was 2×10^{-5} μg/g of sample.

TABLE 6-1. Analytical Methods for Determining Silver in Biological Materials

Sample Matrix	Sample Preparation	Analytical Method	Sample Detection Limit	Accuracy	Reference
Biological tissues	Digest sample with HNO_3; evaporate to dryness; add glacial acetic acid and adjust to pH 3; add ammonium pyrrolidine dithiocarbamate and extract with methyl-isobutyl ketone; heat organic phase to dryness; dissolve residue with HNO_3	GFAAS	0.0012 µg/g (ketone extract) 0.00002 µg/g (extract after reversion to aqueous solution)	No data	Segar and Gilio 1974
Whole blood	Dilute sample with water; agitate in ultrasonic bath and analyze	GFAAS	0.5 µg/100 mL	100-120% recovery	DiVincenzo et al. 1985
	Pipette sample into nickel micro-cup and dry at 150•C	MCAAS	0.27 µg/100 mL	98%-110% recovery	Howlett and Taylor 1978
	Add EDTA solution to sample; dilute sample with triton and ammonium hydrogen phosphate; introduce sample solution into a graphite furnace tube; ash sample at 900•C and atomize at 2,000•C	GFAAS	0.015 µg/100 mL	95%-104.5% recovery	Starkey et al. 1987
	Digest sample with 70% perchloric acid and concentrated HNO_3; evaporate to dryness; add 0.4 M NaI and bismuth solution; heat and analyze	HFP-AES or DCP-AES	0.025 µg/100 mL	90%-110% recovery	Nakashima et al. 1975
	Add EDTA solution to sample; add concentrated HNO_3 and shake vigorously; centrifuge at 5,000 g, separate supernatant and analyze	GFAAS	0.24 µg/100 mL	98% recovery	Vince and Williams 1987
Hair	Wash sample with benzene; filter solution on paper disk and dry disk; insert sample into quartz tube open from both ends; wash sample with water at 50•C and irradiate	NAA	0.69 ppm	No data	Dutkiewicz et al. 1978

TABLE 6-1 (Continued)

Sample Matrix	Sample Preparation	Analytical Method	Sample Detection Limit	Accuracy	Reference
Hair (Cont.)	Wash hair with water and air-dry; digest sample with concentrated HNO_3 by heating; cool sample and dilute to required volume with water	GFAAS	0.02 µg/g	90%-95% recovery	DiVincenzo et al. 1985
Feces	Homogenize sample with water and lyophilize; dissolve ash residue with concentrated H_2SO_4 and HNO_3 and evaporate excess acid to dryness; add HNO_3 and dilute to required volume with water	GFAAS FAAS	0.2 µg/g 3.0 µg/g	80%-100% recovery	DiVincenzo et al. 1985
Liver	Dry sample at 100°C overnight; digest with a mixture of 16 M HNO_3 and 12 M HCl at 100°C; centrifuge and decant supernatant; extract remaining lipid with hot water; cool and recentrifuge; evaporate supernatant to a small volume and dilute with water	FAAS	0.34 µg/g	99%-101% recovery	Johnson 1976
	Ash sample overnight at 450°C with HNO_3; dissolve ash with 50% aqueous HCl; filter sample and analyze at 328.1 nm	AAS	0.0001-0.0005 µg/g	88-92% recovery	Pickston et al. 1983
Pulmonary tissues	Fix tissue sample in 10% buffered formalin for 24 hours; dehydrate in alcohol and embed in paraffin; section sample at 7 microns; stain in hematoxylin and eosin solutions	XES and SEM	Seven-micron-thick sections	No data	Brody et al. 1978
Urine	Evaporate sample to dryness; wet ash residue by heating with concentrated H_2SO_4 and HNO_3 and evaporate excess acid to dryness; add HNO_3 and dilute to required volume with water	GFAAS	0.005 µg/L	110%-130% recovery	DiVincenzo et al. 1985
	Adjust sample to pH 2 with HNO_3 and analyze	GFAAS	1.4 µg/L	99%	Vince and Williams 1987

GFAAS = graphite furnace (flameless) atomic absorption spectroscopy; MCAAS = micro-cup atomic absorption spectroscopy; DCP-AES = direct current plasma-atomic emission spectroscopy; HFP-AES = high frequency plasma-torch-atomic emission spectroscopy; NAA = neutron activation analysis; FAAS = flame atomic absorption spectroscopy; AAS = atomic absorption spectrophotometer; XES = X-ray energy spectrometry; and SEM = scanning electron microscopy.

TABLE 6-2. Analytical Methods for Determining Silver in Environmental Samples

Sample Matrix	Sample Preparation	Analytical Method	Sample Detection Limit	Accuracy	Reference
Simulated solid-waste leaches	Digest sample with a mixture of HNO_3 and HF at 100•C overnight; cool solution and add $HClO_4$; heat until sample is evaporated to dryness; dissolve residue in HCl and water	FAAS	0.568 µg/mL (level 1) 0.473 µg/mL (level 2)	No data	Rains et al. 1984
		DCP-AES	0.53 µg/mL (level 1) 0.38 µg/mL (level 3)	No data	
Rain and stream water	Extract sample with organic solvent; concentrate and analyze atom	GFAAS	ng/mL range	No data	Rattonetti 1974
Fresh water	Add 2% citric acid solution to sample and evaporate solution; add buffer (pH 7.2) and react with succinate dehydrogenase -- chromogenic complex solution	Paper chromatography or micro TLC	1 µg/sample	No data	Devi and Kumar 1981
Commercial condensed milk	Digest sample with 70% perchloric acid and concentrated HNO_3 solution, evaporate solution to almost dryness; dissolve residue in water and add 0.4 M NaI and bismuth solution; heat and analyze	HFP-AES or DCP-AES		89%-94% recovery	Nakashima et al. 1975
Air	Collect sample through a Delbag Mikrosorban filter or General Electric filter; store sample in sealed polyethylene bag; irradiate sample and analyze	NAA	0.13 µg/10 cm^2 (Delbag Mikrosorban filter); 0.008 µg/10 cm^2 (General Electric filter)	No data	Bogen 1973
	Calibrate sampling pump; collect sample at known flow rate; add concentrated HNO_3 and $HClO_4$; heat sample solution to dryness; dissolve residue ash in 4% HNO_3 and 1% $HClO_4$ solution; analyze at 328.3 nm	ICP-AES	26 ng/mL	91%-111% recovery	NIOSH 1984b (method 7300)

TABLE 6-2 (Continued)

Sample Matrix	Sample Preparation	Analytical Method	Sample Detection Limit	Accuracy	Reference
	Collect sample at rate of 20 liter/min using acetyl-cellulose filter and analyze at 328 nm	AAS	$3x10^{-4}$ mg/mL	No data	Soldatenkova and Smirnov 1983
	Filter particulate matter from air; irradiate and count sample	NAA (nondestructive)	0.1 μg/sample	No data	Dams et al. 1970
Raw beef	Prepare ash of sample by heating to 500•C; hydrolyze ash sample with 6 N H_2SO_4 and adjust pH to 1.8-2.0; add 2 N ammonium acetate solution and stir overnight; centrifuge and analyze	GSE	0.013 ppm	No data	Mitteldorf and Landon 1952
Waste water	Digest sample and add 5% potassium citrate, phenolphthalein indicator, and 4 M NaOH until solution turns red; add HNO_3 to decolorize solution; finally add buffer (pH 5), 0.1 M EDTA, 1% sodium lauryl sulfate and 0.5 m/g (3,5-diBr-PADAP) in ethanol; measure absorbance at 570 nm	UV	0.39 ppm	>90% recovery	Hung et al. 1982
Metallic silver	Add 0.3 N HNO_3 to sample and adjust to pH 2.3; extract sample with an automated extraction system	FAAS	0.4 μg/L	No data	Pierce et al. 1975
Eye lotion	Add silver nitrate sample to 95% HNO_3 solution and heat to 80-90•C while agitating; cool and filter solution; react filtrate by shaking with a solution of 0.2% dithizone in chloroform; analyze silver in silver nitrate solution at 400 nm	PD	50 ppm	4% error	Massa 1969

FAAS = flame atomic absorption spectroscopy; DCP-AES = direct current plasma-atomic emission spectroscopy; GFAAS = graphite furnace (flameless) atomic absorption spectroscopy; TLC = thin layer chromatography; HFP-AES = high frequency plasma-atomic emission spectroscopy; NAA = neutron atomic analysis; ICP-AES = inductively coupled plasma-atomic emission spectroscopy; AAS = atomic absorption spectrometry; GSE = graphite spectroscopic electrode; UV = ultraviolet spectrophotometry; PD = photodensitometer; and (3,5-diBr-PADAP) = 2(-3,5-dibromo-2-pyridylazo)-5-diethyl-aminophenol.

Recently, Starkey et al. (1987) modified the GFAAS technique for determining trace levels of silver in the blood of exposed and unexposed individuals. Ethylene diamine tetraacetic acid (anticoagulant) and ammonium hydrogen phosphate buffer (matrix modifier) were added to blood samples prior to analysis. Starkey and co-workers indicated that the GFAAS technique is highly selective and sensitive and does not require a complex sample pretreatment (ashing and digestion with strong acids). A detection limit of 15×10^{-3} μg/100 mL of sample was reported.

Howlett and Taylor (1978) used an atomic absorption spectroscopy fitted with a micro-cup assembly (MCAAS) for determining silver levels in human whole blood. The MCAAS technique affords a rapid, precise, and relatively simple method for the measurement of silver in blood. Furthermore, this technique requires no sample preparation prior to analysis except pipetting and drying. A detection limit level of 0.27 μg/100 mL of blood sample was measured. Howlett and Taylor (1978) noted that repeated measurement of silver in blood using a single nickel cup showed a gradual decrease in sensitivity.

FAAS technique has been successfully used to detect levels of silver in post-mortem human liver; the detection limit for this method was 0.34 μg/g (Johnson 1976).

HFP-AES can determine ng amounts of silver in a small sample of human blood. Prepared human blood sample was introduced into the atomizer chamber as an aerosol, formed by nebulization of the sample solution (Nakashima et al. 1975). The authors noted that the sensitivity of the HFP-AES technique was improved by eliminating moisture in the aerosol with a second condenser at -3 to -5°C. The use of bismuth as a coprecipitate showed an enhancing effect on the silver emission at 328.06 nm. A detection limit of 0.25 μg/100 mL of sample was attainable. Advantages of the HFP-AES methodology include freedom from most types of chemical interference, high sensitivity, and multi-elemental capability. However, this technology might have to be adapted to currently available instrumentation in order to be useful. The presence of spectral interferences is a disadvantage of plasma emission spectroscopy. These interferences are caused when a sample contains elements that have analytical emission lines that overlap the line chosen for the analyte. Blood is particularly troublesome because of high concentration of iron. Iron has a very complex emission spectrum. Also, the analytical line for silver used in the Nakashima et al. paper has interference from manganese. For this reason, the blood is subjected to dangerous perchloric acid/nitric acid digestion and preconcentration of silver ion prior to analysis. Other inherent disadvantages of HFP-AES include the employment of time-consuming procedure, the need for standard additions for accurate quantification, and its high costs when compared to GFAAS. Unless a laboratory is already furnished with the instrumentation, purchase of HFP-AES is not recommended for the analysis of silver alone. GFAAS or even DCP-AES could be employed for the determination of silver in biological samples.

6. ANALYTICAL METHODS

Owing to its high sensitivity, the NAA technique has been widely employed for determination of trace elements (including silver) in biological and environmental samples. The NAA technique is based on interaction of the nuclei of individual silver atoms of the sample with neutron irradiation, resulting in the emission of γ-rays (photons). The radioactivity of the irradiated sample is measured with a high-resolution lithium-drifted germanium detector. The long-lived, metastable ^{110m}Ag isotope of silver was formed following irradiation of human hair samples. A half-life of 250.4 days for ^{110m}Ag gives ample time to initiate counting after an irradiation and cooling period (Dutkiewicz et al. 1978). The authors noted a detection limit for silver of 0.69 ppm in human hair. (See Section 2.5 for a discussion of the disadvantages of using hair samples for monitoring exposure to silver.) A disadvantage of NAA is that it is a very expensive technique and may not be readily available in most laboratories.

DiVincenzo et al. (1985) employed the GFAAS technique to evaluate human samples for biological monitoring of silver exposure levels in the workplace. The authors determined the total silver concentration in urine, blood, feces, and hair with detection limits of 0.005 μg/L, 0.5 μg/100 mL, 0.2 μg/g, and 0.02 μg/g, respectively.

Scanning electron microscopy (SEM) in concert with x-ray energy spectrometry (XES) has been used to detect silver in pulmonary, lacrimal sac, and skin tissues of individuals with diffuse interstitial lung disease, chronic dacryocystitis, and skin disorders, respectively (Brody et al. 1978; Loeffler and Lee 1987; Tanita et al. 1985). Brody et al. (1978) observed particles of preselected lesions of human pulmonary tissue magnified to 300x by SEM, and the silver content was analyzed by XES. The authors noted that SEM and XES techniques permit a rapid and conclusive determination of silver, silver compounds, and complexes in tissue lesions.

6.2 ENVIRONMENTAL SAMPLES

Atomic absorption and plasma emission spectroscopy are perhaps the most widely used analytical techniques for the determination of silver levels in air, soil, and water.

Rains et al. (1984) employed atomic absorption spectroscopy with flame atomization (FAAS) and direct current plasma-atomic emission spectroscopy (DCP-AES) to determine silver levels in solid-waste leachate. In the FAAS technique, a diluted solution of the sample following ashing and digestion is sprayed into a flame by means of a nebulizer. The high temperature causes formation of atoms, which can be observed (at 328.1 nm resonance line) by absorption spectroscopy. The authors noted that interference encountered by the FAAS technique was largely alleviated by the use of 1% solution of ammonium dibasic phosphate buffer as a matrix modifier. In the DCP-AES technique, Rains and co-workers observed silver as a broad band emission at 328.068 nm resonance line. Addition of lithium carbonate to sample solution

reduces the inter-element interferences observed in unbuffered direct-current plasmas, but does not significantly degrade DCP-AES detection limits. Detection limits of silver in solid-waste leachate sample by FAAS and DCP-AES techniques were 0.473×10^{-6} g/mL sample and 0.38×10^{-6} g/L sample, respectively (Rains et al. 1984).

GFAAS technique is more sensitive than FAAS methodology for determination of silver in water samples. Rain and stream water have been analyzed by GFAAS technique to detect silver at ng/mL levels (Rattonetti 1974).

Inductively coupled argon plasma with atomic emission spectroscopy (ICP-AES) has been recommended by NIOSH (method 7300) for determining silver in air. ICP-AES offers multi-element capabilities and high sensitivity but spectral (background) interference can be a problem (NIOSH 1984b). The EPA-established analytical test procedure (method 200.7) to analyze dissolved, suspended or total silver in drinking water, surface water, and domestic and industrial wastewaters employs the ICP-AES technique (EPA 1987a). An estimated detection limit of 7.0×10^{-6} g silver/L sample was measured.

Neutron activation analysis (NAA) methodology has been used to determine silver levels in environmental samples. Bogen (1973) reported a detection limit of 8×10^{-9} g silver/10 cm^2 filter. The author indicated that the use of high-resolution lithium-drifted-germanium detection allows multi-elemental analysis to be performed in a single measurement without any chemical pretreatment of the air sample. A highly precise, sensitive, and nondestructive computer-assisted NAA technique for the determination in air of multi-element particulate matter has been designed by Dams et al. (1970). The authors reported a detection limit of 1×10^{-7} g silver/sample. The NAA technique by Bogen (1973) and Dams et al. (1970), utilizes the long-lived isotope of silver (^{110m}Ag) for quantifying silver levels in air. The faster nondestructive NAA technique developed by Dams et al. (1970) utilizes the short-lived isotope ^{110}Ag (half-life = 24.6 seconds) to detect silver in air following an 18-second neutron irradiation of air sample. Hence, counting can be initiated after an irradiation and cooling period of a few minutes.

Hung et al. (1982) developed a sensitive and selective method for silver analysis by reacting silver (I) with 2(-3,5-dibromo-2-pyridylazo)-5-diethyl amino phenol in the presence of an anionic surfactant, sodium lauryl sulfate. The ternary complex formed is red and exhibits an absorption peak at 570 nm. Hung and his co-workers employed EDTA as a chelating agent, thereby reducing the interference of common ions. Recoveries were good, and a detection limit of 0.39 ppm of silver was achieved.

Paper chromatographic, micro thin-layer chromatographic (TLC) and photodensitometric (PD) methods have also been successfully used to determine levels of silver compounds in freshwater and eye lotion samples (Devi and Kumar 1981; Massa 1969). Simple paper and micro thin layer chromatographic (TLC) techniques were employed by Devi and Kumar (1981) to detect and quantify

trace (40 ppm) levels of silver nitrate in fresh water. Devi and Kumar reacted a prepared silver nitrate sample with succinate dehydrogenase enzyme-chromogenic reagent complex solution prior to paper chromatographic or micro TLC analysis. The metals are recognized by their ability to inhibit the enzymatic formation of a pink reaction product.

Soil samples have been analyzed for silver by AAS (Klein 1972), NAA, and x-ray fluorescence analysis (Ragaini et al. 1977). No statements on the sensitivity, accuracy, or precision of these methods for soil analysis were presented in the brief description of these methods.

6.3 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.

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Existing methods of measuring levels of silver in blood, urine, feces, hair, and tissues are extremely sensitive and can measure levels in the low ppm to ppt. These methods are accurate and reliable and can be used to measure both background levels of exposure and levels at which biological effects occur. No additional analytical methods for determining trace levels of silver in biological materials are needed.

Highly sensitive methods exist to measure silver concentrations in blood, urine, hair, and skin samples of individuals showing the few health effects that have been associated with silver exposure. These methods are also able to accurately measure background levels in the population. No additional analytical methods appear to be needed for the known biomarkers of effect.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Sophisticated and highly refined methods are available

to detect trace levels of silver and its compounds in air, solid waste leachate, water (the medium of most concern for human exposure), food, and other environmental media. These methods can accurately measure background levels in environmental samples, as well as levels at which health effects occur. There are no known deficiencies in the analytical methods for determining silver in environmental media, and no additional analytical methods appear to be necessary.

6.3.2 On-Going Studies

No on-going studies concerning techniques for measuring and determining silver in biological and environmental samples were located.

7. REGULATIONS AND ADVISORIES

Silver is on the list of chemicals appearing in "Toxic Chemicals Subject to Section 313 of the Emergency Planning and Community Right-to-Know Act of 1986" (EPA 1987b).

No international regulations pertaining to silver were found. The national and state regulations and guidelines regarding silver in air, water, and other media are summarized in Table 7-1.

7. REGULATIONS AND ADVISORIES

TABLE 7-1. Regulations and Guidelines Applicable to Silver

Agency	Description	Value	Reference
	National		
Regulations:			
a. Air:			
OSHA	PEL TWA (metal and soluble compound)	0.01 mg/m^3	OSHA 1988b (29 CFR 1910.1000)
b. Water:			
EPA ODW	Drinking water MCL[a]	0.05 mg/L	EPA 1987d (40 CFR 141)
	Proposed drinking water SMCL	0.09 mg/L	EPA 1989b
FDA	Permissible levels in bottled water	0.05 mg/L	FDA 1988a (21 CFR 103.35)
c. Other:			
EPA OSW	Silver nitrate designated as hazardous waste substance	No data	EPA 1987a (40 CFR 116.4)
EPA OERR	Reportable Quantity (RQ)		EPA 1988b (40
	(silver and compounds)	1000 lb	CFR 302.4)
	(silver nitrate)	1 lb	
EPA OTS	Toxic chemical release reporting; community right-to-known (proposed) (silver and compounds)	No data	EPA 1987b (52 FR 21152)
OSHA	Meets proposed medical records rule	No data	OSHA 1988a (29 CFR 1910.20)
Guidelines:			
a. Air:			
ACGIH	TLV TWA:		
	Silver metal dust	0.1 mg/m^3	ACGIH 1986
	Airborne soluble silver compounds	0.01 mg/m^3	
NIOSH	Recommended exposure limit	0.01 mg/m^3	NIOSH 1985
NIOSH	IDLH (silver and soluble silver compounds)	0.01 mg/m^3	NIOSH 1985
b. Water:			
EPA ODW	Recommended drinking water limits	0.05 mg/L	EPA 1985a
EPA OWRS	Ambient water quality criteria to protect human health ingesting water and organisms	0.05 mg/L	EPA 1980b (45 FR 79318)
c. Other:			
EPA	RfD (oral)	3x10^{-3} mg/kg/day	IRIS 1989
EPA ODW	Carcinogen classification	Group D[b]	EPA 1988a
	State		
	Regulations:		
a. Water:	Maximum concentration levels in drinking water:	0.05 mg/L	CELDS 1988
Alabama			
Alaska			
Arkansas			
Arizona			
California			
Colorado			
Connecticut			
Delaware			
District of Columbia			
Florida			
Hawaii			

TABLE 7-1 (Continued)

Agency	Description	Value	Reference
Idaho			
Illinois			
Indiana			
Kansas			
Kentucky			
Louisiana			
Maine			
Maryland			
Massachusetts			
Michigan			
Mississippi			
Minnesota			
Missouri			
Montana			
Nebraska			
Nevada			
New Hampshire			
New Mexico			
New York			
North Carolina			
North Dakota			
Ohio			
Oklahoma			
Oregon			
Pennsylvania			
Rhode Island			
South Carolina			
South Dakota			
Tennessee			
Texas			
Utah			
Vermont			
Virginia			
Washington			
West Virginia			
Wisconsin			
Wyoming			
	Groundwater concentration limits[c]:	0.05 mg/L	CELDS 1988
Colorado			
Indiana			
Kentucky			
Massachusetts			
Nevada			
New Mexico			
New York			
Wisconsin		0.05 mg/L	WDHSS 1989

7. REGULATIONS AND ADVISORIES

TABLE 7-1 (Continued)

Agency	Description	Value	Reference
Arizona Mississippi New Jersey New York South Dakota Virginia	Water quality criteria[d]	0.05 mg/L	CELDS 1988

[a]The EPA has proposed to delete the MCL for silver (EPA 1989b).
[b]Group D. Not classifiable as to carcinogenicity in humans.
[c]The classification of groundwater by future use may vary between states.
[d]The criteria upon which this value is based may vary between states, e.g., recreation aquatic life, etc.

ACGIH = American Conference of Government Industrial Hygienists; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; IDLH = Immediately Dangerous to Life or Health; MCL = Maximum Contaminant Level; NIOSH = National Institute for Occupational Safety and Health; ODW = Office of Drinking Water; OERR = Office of Emergency and Remedial Response; OSHA = Occupational Safety and Health Administration; OSW = Office of Solid Wastes; OTS = Office of Toxic Substances; OWRS = Office of Water Regulations and Standards; PEL = Permissible Exposure Limit; RfD = Reference Dose; RQ = Reportable Quantity; SMCL = Secondary Maximum Contaminant Level; TLV = Threshold Limit Value; TWA = Time-Weighted Average

8. REFERENCES

*Aaseth J, Olsen A, Halse J, et al. 1981. Argyria-tissue deposition of silver as selenide. Scand J Clin Lab Invest 41:247-251.

Abdel Rahim AG. 1985. The effects of dietary L-ascorbic acid on the absorption and utilization of Na75Se03 of silver-treated rats. Comp Biochem Physiol 81C:131-132.

*ACGIH. 1986. Documentation of the threshold limit values and biological exposure indices. 5th ed. American Conference of Governmental Industrial Hygienists, Inc., Cincinnati, OH, 529.

*Alexander J, Aaseth J. 1981. Hepatobiliary transport and organ distribution of silver in the rat as influenced by selenite. Toxicology 21:179-186.

Alexander J, Aaseth J, Refsvik T. 1980. Biliary excretion of glutathione in the rat-significance for the biliary excretion of heavy metals [Abstract]. Naunyn-Schmiedeberg Arch Pharmacol 313:R66.

Andelman JB. 1973. Incidence, variability and controlling factors for trace elements in natural, fresh waters. In: Singer PC, ed. Trace metals and metal-organic interactions in natural waters. Ann Arbor, MI: Ann Arbor Science Publishers Inc., 57-88.

*Anderson JB, Jenne EA, Chao TT. 1973. The sorption of silver by poorly crystallized manganese oxides. Geochimica et Cosmochimica Acta 37:611-622.

Anghileri LJ. 1968. In vivo and in vitro deiodination of silver iodide. Experientia 24:895.

Anghileri LJ. 1969. Studies on the in vivo breakdown of insoluble halides. Acta Isotope 9:347-356.

Aoki K, Hori J, Kawashima K. 1967. Effect of metallic cations on human serum: Study by starch-gel electrophoresis. II Effect of Hg++, Cr+++, Ag+, Ni++, Cd++, Zn++, Ba++, Mg++, Al+++ and Fe+++. Arch Biochem Biophys 120:255-267.

---

*Cited in text.

8. REFERENCES

Aronstam RS, Eldefrawi ME. 1979. Transition and heavy metal inhibition of ligand binding to muscarinic acetylcholine receptors from rat brain. Toxicol Appl Pharmacol 48:489-496.

Baba S, Shinohara Y, Sano H, et al. 1984. Application of high-performance liquid chromatography with synchronized accumulating radioisotope detector to analysis of glyceryl trinitrate and its metabolites in rat plasma. J Chromatog 305:119-126.

*Bader KF. 1966. Organ deposition of silver following silver nitrate therapy of burns. Plast Reconstr Surg 37:550-551.

*Baes CF III, Sharp RD. 1983. A proposal for estimation of soil leaching and leaching constants for use in assessment models. J Environ Qual 12:17-28.

Bailey JA, Jones AM, Roy DR. 1973. Effects of silver from cloud seeding on microflora of animal digestive systems. Report to US Bureau of Reclamation, Division of Atmospheric Water Resources Management, Denver, CO, by Department of Fishery and Wildlife Biology, Colorado State University, Fort Collins, CO. NTIS PB226-062.

Ballinger PM, Brown BS, Griffin MM, et al. 1982. Evidence for carriage of silver by sulphadimidine: Hemolysis of human erythrocytes. Br J Pharmacol 77:141-145.

*Bard CC, Murphy JJ, Stone DL, et al. 1976. Silver in photoprocessing effluents. Water Pollut Cont Fed 48:389-394.

*Barnes D, Bellin J, DeRosa C, et al. 1987. Reference dose (RfD): Description and use in health risk assessments. Appendix A: Integrated risk information system supportive documentation. Washington, DC: US Environmental Protection Agency, Office of Health and Environmental Assessment. EPA/600/8-86-032a.

Barrie HJ, Harding HE. 1947. Argyro-siderosis of the lungs in silver finishers. Brit J Industr Med 4:225-232.

*Becker RO. 1987. The effect of electrically generated silver ions on human cells. In: Proceedings of the First International Conference on Gold and Silver in Medicine, Bethesda, Maryland, May 13-14, 1987. Washington, DC: The Gold and Silver Institutes, 227-243.

*Becker RO, Spadaro JA. 1978. Treatment of orthopedic infections with electrically generated silver ions. The Journal of Bone and Joint Surgery 60-A:871-881.

8. REFERENCES

Bergmann M, Engel C. 1968. [Silver deposits in the gastric mucosa and liver in universal argyrosis due to treatment with tragesine]. Dtsch Gesundheitsw 23:629-31. (German).

*Berry JP, Galle P. 1982. Selenium and kidney deposits in experimental argyria. Electron microscopy and microanalysis. Pathol Biol (Paris) 30:136-140.

Bertine KK, Goldberg ED. 1971. Fossil fuel combustion and the major sedimentary cycle. Science 173:233-235.

Bertine KK, Goldberg ED. 1972. Trace elements in clams, mussels, and shrimp. Limnology Oceanography 17:877-884.

Bessing C, Kallus T. 1987. Evaluation of tissue response to dental alloys by subcutaneous implantation. Acta Odontol Scand 45:247-255.

Biddinger GR, Gloss SP. 1984. The importance of trophic transfer in the bioaccumulation of chemical contaminants in aquatic ecosystems. Resi Rev 91:103-145.

Blaha K Jr, Havrdova J, Rosina J, et al. 1987. The effect of 110mAg on ceruloplasmin oxidase activity in rats. J Hyg Epidemiol Microbiol Immunol 31:39-43.

*Bleehen SS, Gould DJ, Harrington CI, et al. 1981. Occupational argyria; light and electron microscopic studies and x-ray microanalysis. Br J Dermatol 104:19-26.

*Blumberg H, Carey TN. 1934. Argyremia: Detection of unsuspected and obscure argyria by the spectrographic demonstration of high blood silver. J Am Med Assoc 103:1521-1524.

*Bogen J. 1973. Trace elements in atmospheric aerosol in the Heidelberg area, measured by instrumental neutron activation analysis. Atmos Environ 7:1117-1125.

Boissevain CH, Drea WF. 1936. Relation between the occurrence of endemic goiter and the presence of traces of silver and barium in drinking water. Endocrinology 26:686-687.

Bourdon-Ranisteano S, Bourdon R, Prouillet F. 1977. [Determination of silver in biological materials]. Ann Biol Clin 35:397-400. (French).

*Boyle RW. 1968. Geochemistry of silver and its deposit notes on geochemical prospecting for the element. Geological Survey of Canada. Ottawa, Ont: Canada, Department of Energy, Mines and Resources. 160., 1-96.

8. REFERENCES

Bradford GR, Bair FL, Hunsaker V. 1968. Trace and major element content of 170 High Sierra Lakes in California. Limnology and Oceanography 13:526-530.

Braidech MM, Emery FH. 1935. The spectrographic determination of minor chemical constituents in various water supplies in the United States. J Amer Water Works Assoc 27:557-580.

Brar SS, Nelson DM, Kline JR, et al. 1970. Instrument analysis for trace elements present in Chicago area surface air. Journal of Geophysics Research 75:2939-2945.

Braunstein HM, Pack DJ, Oakes TW. 1982. Intercomparison of stable element content of foods by statistical methods. Proc Univ MO Annu Conf Trace Subst Environ Health. 16:377-390.

Breton J, Foncin JF, Caroff J, et al. 1971. [Argyria and argyrism: Two unusual cases. Value of electron microscopy and derived methods]. Med Leg Dommage Corp 4:245-248. (French).

*Brody AR, Vallyathan NV, Craighead JE. 1978. Use of scanning electron microscopy and x-ray energy spectrometry to determine the elemental content of inclusions in human tissue lesions. Scanning Microsc 2:615-622.

Brooks SM. 1981. Lung disorders resulting from the inhalation of metals. Clin Chest Med 2:235-254.

Brooks SM. 1986. Pulmonary reactions to miscellaneous mineral dusts, man-made mineral fibers, and miscellaneous pneumoconioses. In: Merchant JA, ed. Occupational respiratory diseases. Morgantown, WV: US Department of Health and Human Services, Division of Respiratory Disease Studies, 401-458.

Brozman M, Chorvath D, Jakubovsky J. 1976. [Localization of silver in glomerular basement membranes in experimental argyrosis]. Bratisl Lek Listy 66:253-263. (Polish).

Bruevich TS, Bogomolets NN, Berezovskii AD. 1980. [Sensitizing action of precious metal compounds: Gold, platinum, ruthenium, rhodium and silver]. Gig Tr Prof Zabol:42-44. (Russian).

Brulaud KW, Bertine K, Koide M, et al. 1974. History of metal pollution in the Southern California coastal zone. Environ Sci Technol 8:425-432.

Brune D, Beltesbrekke H. 1979. Levels of mercury and silver in dust from the trimming of amalgam dies. Scand J Dent Res 87:462-465.

8. REFERENCES

Brune D, Nordberg G, Wester PO. 1980. Distribution of 23 elements in the kidney, liver and lungs of workers from a smeltery and refinery in north Sweden exposed to a number of elements and of a control group. The Science of the Total Environment 16:13-35.

*Buckley WR. 1963. Localized argyria. Arch Dermatol 88:531-539.

Buckley WR, Terhaar CJ. 1973. The skin as an excretory organ in argyria. Trans St John's Hosp Dermatol Soc 59:39-44.

*Buckley WR, Oster CF, Fassett DW. 1965. Localized argyria: II. Chemical nature of the silver containing particles. Arch Dermatol 92:697-705.

*Bunch RL. 1982. Sewage sludge dilemma of the eighties. In: Pawlowski L, ed. Physiochemical methods for water and wastewater treatment. Amsterdam: Elsevier, 69-81.

*Bunyan J, Diplock AT, Cawthorne MA, et al. 1968. Vitamin E and stress. 8. Nutritional effects of dietary stress with silver. Br J Nutr 22:165-182.

Butt EM, Nusbaum RE, Gilmour TC, et al. 1964. Trace metal levels in human serum and blood. Arch Environ Health 8:60-65.

*Byrne CJ, DeLeon JR. 1986. Trace metal residues in biota and sediments from Lake Pontchartrain, Louisiana. Bull Environ Contam Toxicol 37:151-158.

Cabe PA, Carmichael NG, Tilson HA. 1979. Effects of selenium, alone and in combination with silver or arsenic, in rats. Neurobeh Toxicol 1:275-278.

Caffee HH, Bingham HG. 1982. Leukopenia and silver sulfadiazine. J Trauma 22:586-587.

*Calabrese A, MacInnes JR, Nelson DA, et al. 1984. Effects of long-term exposure to silver or copper on growth, bioaccumulation and histopathology in the blue mussel Mytilus edulis. Marine Environmental Research 11:253-274.

*Callahan MA, Slimak MW, Gabel NW, et al. R; 1979. Water-related environmental fate of 129 priority pollutants. EPA-440/4-79-029a,b.

Camner P, Lundborg M, Hellstrom P. 1974. Alveolar macrophages and 5 μm particles coated with different metals. Arch Environ Health 29:211-213.

Camner P, Hellstrom PA, Lundborg M, et al. 1977. Lung clearance of 4-μm particles coated with silver, carbon, or beryllium. Arch Environ Health 32:58-62.

8. REFERENCES

Carson BL, Ellis HV III, McCann JL. 1986. Toxicology and biological monitoring of metals in humans. Chelsea, MI: Lewis Publishers, Inc., 219-225.

*Casto BC, Meyers J, DiPaolo JA. 1979. Enhancement of viral transformation for evaluation of the carcinogenic or mutagenic potential of inorganic metal salts. Cancer Res 39:193-198.

*Catsakis LH, Sulica VI. 1978. Allergy to silver amalgams. Oral Surg 46:371-375.

CELDS. 1989. Computer-Environment Legislative Data Systems. The Environmental Technical Information System (ETIS). Department of Urban and Regional Planning, Planning Information Program, University of Illinois, Urbana-Champaign, IL. January 6, 1989.

Cerrai E, Ghersini G. 1966. Reversed-phase paper chromatography of some cations with two nitrophenylthiophosphate derivatives as stationary phases. J Chromatogr 22:425-430.

Charley RC, Bull AT. 1979. Bioaccumulation of silver by a multispecies community of bacteria. Arch Microbiol 123:239-244.

*CHEMLINE. 1988. National Library of Medicine, National Toxicology Information Program, Bethesda, MD. December 5, 1988.

Cherian MG, Goyer RA. 1978. Role of metallothioneins in disease. Ann Clin Lab Sci 8:91-94.

Chien PT. 1979. Metallic copper and silver dust hazards... [editorial]. Am Ind Hyg Assoc J 40:747-748.

*CHMR. 1989. Hazardous waste minimalization manual for small quantity generators. Center for Hazardous Materials Research, University of Pittsburgh Applied Research Center, Pittsburgh, PA.

Chorvath D, Brozman M, Jakubosky J. 1976. [Morphology of experimental argyrosis in kidneys]. Cesk Patol 4:161-165. (Czech).

CCRIS. 1988. Chemical Carcinogenesis Research Information System. Chemical Information System (CIS). December 5, 1988.

Clemente GF, Cigna Rossi L, Santaroni GP. 1977. Trace element intake and excretion in the Italian population. J of Radioanal Chem 37:549-558.

8. REFERENCES

*Coffin DL, Palekar LD. 1985. Bioassays for asbestos and other solid materials. In: Milman HA and Weisburger EK, ed. Handbook of Carcinogen Testing. Park Ridge, NJ: Noyes Publications, 384-419.

Coglianese MP, Martin M. 1981. Individual and interactive effects of environmental stress on the embryonic development of the pacific oyster, Crassostrea gigas. I. The toxicity of copper and silver. Mar Environ Res 5:13-27.

*Cole RJ, Frederick RE, Healy RP, et al. 1984. Preliminary findings of the priority pollutant monitoring project of the nationwide urban runoff program. Water Pollut Cont Fed 56:898-908.

*Coleman RL, Cearley JE. 1974. Silver toxicity and accumulation in largemouth bass and bluegill. Bull Environ Contam Toxicol 12:53-61.

Connors RC, Daniels F Jr. 1973. Generalized argyria. Cutis 11:796-801.

*Constable J, Morris P, Burke J. 1967. Absorption pattern of silver nitrate from open wounds. Plast Reconst Surg 39:342-348.

*Contract Laboratory Program Statistical Database. 1988. US Environmental Protection Agency, Contract Laboratory Program, Washington, DC.

*Cooper CF, Jolly WC. 1970. Ecological effects of silver iodide and other weather modification agents. Water Resource Research 6:88-98.

Costello J. 1983. Mortality of metal miners a retrospective cohort and case control study. In: Wagner WL, Rom WN, Merchant JA, eds. Health issues related to metal and nonmetallic mining. Boston, MA: Butterworth Publishers, 227-240.

*Creasey M, Moffat DB. 1973. The deposition of ingested silver in the rat kidney at different ages. Experientia 29:326-327.

Creason JP, Hinners TA, Bumgarner JE, et al. 1975. Trace elements in hair, as related to exposure in metropolitan New York. Clin Chem 21:603-612.

*Creason JP, Svendsgaard D, Bumgarner J, et al. 1976. Maternal-fetal tissue levels of 16 trace elements in 8 selected continental United States communities. Proc Univ MO Annu Conf Trace Subst Environ Health. 10:53-62.

*Cunningham WC, Stroube WB Jr. 1987. Application of an instrumental neutron activation analysis procedure to analysis of food. Sci Total Environ 63:29-43.

8. REFERENCES

Curtin GC, King HD, Mosier EL. 1974. Movement of elements into the atmosphere from coniferous trees in subalpine forests of Colorado and Idaho. Journal of Geochemical Exploration 3:245-263.

*Dams R, Robbins JA, Rahn KA, et al. 1970. Non destructive neutron activation analysis of air pollution particulates. Anal Chem 42:861-867.

*Dams R, Billet J, Hoste J. 1975. Neutron activation analysis of F, Sc, Se, Ag, and Hf, in aerosols using short-lived isotopes. Int J Environ Anal Chem 4:141-153.

*Danscher G. 1981. Light and electron microscopic localization of silver in biological tissue. Histochemistry 71:177-186.

*Davidson CI, Goold WD, Mathison TP, et al. 1985. Airborne trace elements in Great Smoky Mountains, Olympic, and Glacier National Parks. Environ Sci Technol 19:27-35.

Davies PH, Goettl JP Jr, Sinley JR. 1978. Toxicity of silver to rainbow trout (Salmo gairdneri). Water Research 12:113-117.

*Day WA, Hunt JS, McGiven AP. 1976. Silver deposition in mouse glomeruli. Pathology 8:201-204.

Deby C, Bacq ZM, Simon D. 1973. In vitro inhibition of the biosynthesis of a prostaglandin by gold and silver. Biochem Pharmacol 22:3141-3143.

*Demerec M, Bertani G, Flint J. 1951. A survey of chemicals for mutagenic action on E. coli. The American Naturalist 85:119-136.

*Dequidt J, Vasseur P, Gromez-Potentier J. 1974. [Experimental toxicological study of some silver derivatives]. Bulletin de la Societe de Pharmacie de Lille 1:23-35. (French).

*Devi YP, Kumar NV. 1981. Simple paper and micro thin layer chromatographic method for separation and detection of mercuric chloride, copper sulfate, cadmium sulfate, and silver nitrate in fresh water. J Assoc Off Anal Chem 64:1301-1304.

Dick WA, Bonta JV, Haghiri F, et al. 1983. Stream water quality of two small watersheds as affected by surface coal mining. J Environ Qual 12:351-358.

Dillard CJ, Tappel AL. 1986. Mercury, silver, and gold inhibition of selenium-accelerated cysteine oxidation. J Inorg Biochem 28:13-20.

8. REFERENCES

Diplock AT, Green J, Bunyan J, et al. 1967. Vitamin E and stress. 3. The metabolism of D-alpha-tocopherol in the rat under dietary stress with silver. Br J Nutr 21:115-125.

Diplock AT, Baum H, Lucy JA. 1971. The effect of vitamin E on the oxidation state of selenium in rat liver. Biochem J 123:721-729.

Dissanayake CB, Tobschall HJ, Palme H, et al. 1983. The abundance of some major and trace elements in highly polluted sediments from the Rhine river near Mainz, West Germany. Sci Total Environ 29:243-260.

*DiVincenzo GD, Giordano CJ, Schriever LS. 1985. Biologic monitoring of workers exposed to silver. Int Arch Occup Environ Health 56:207-215.

*Domsch KH. 1984. Effects of pesticides and heavy metals on biological processes in soil. Plant Soil 76:367-378.

*Douglas WJ. 1968. Toxic properties of materials used in weather modification. Proceedings of the first national conference on weather modification. Boston, MA: American Meteorological Society, 351-360.

*Drake HJ. 1980. Silver. Mineral facts and problems. Washington, DC: U.S. Department of the Interior, Bureau of Mines. Preprint from Bulletin 671.

Dreisback RH, Robertson WO, ed. 1977. Handbook of poisoning: Prevention, diagnosis and treatment. 12th ed. Los Altos, CA: Lang Medical Publications, 373-376.

*Dubin NH, Parmley TH, Cox RT, et al. 1981. Effect of silver nitrate on pregnancy termination in cynomolgus monkeys. Fertil Steril 36:106-109.

Dunn JA, Holland KB, Jezorek JR. 1987. Argentation liquid chromatography of polynuclear aromatic hydrocarbons on a silver(I)-loaded mercaptopropyl silica gel stationary phase. J Chromatog 394:375-381.

Dupont T, Gomez J, Cuvillier P, et al. 1984. [Drug-induced generalized argyria. Value of blood and urine analysis. Apropos of 2 cases]. IARC Medical 4:103-105. (French).

*Dutkiewicz T, Paprotny W, Sokolowska D, et al. 1978. Trace element content of human hair determined using neutron activation analysis as monitor of exposure effects to environmental metals. Chemia Analityczna 23:261-272.

Dyck W. 1967. Adsorption and coprecipitation of silver on hydrous ferric oxides. Can J Chem 46:1441-1444.

8. REFERENCES

Dymond AM, Kaechele LE, Jurist JM, et al. 1970. Brain tissue reactions to some chronically implanted metals. J Neurosurg 33:574-580.

*East BW, Boddy K, Williams ED, et al. 1980. Silver retention, total body silver and tissue silver concentrations in argyria associated with exposure to an anti-smoking remedy containing silver acetate. Clin Exp Dermatol 5:305-311.

Eaton DL. 1985. Effects of various trace metals on the binding of cadmium to rat hepatic metallothionein determined by the cd/hemoglobin affinity assay. Toxicol Appl Pharmacol 78:158-162.

Eaton DL, Stacey NH, Wong K-L, et al. 1980. Dose-response effects of various metal ions on rat liver metallothionein, glutathione, heme oxygenase and cytochrome P-450. Toxicol Appl Pharmacol 55:393-402.

*Eckel WP, Jacob TA. 1988. Ambient levels of 24 dissolved metals in US surface and ground waters. American Chemical Society, Annual Meeting, Los Angeles, CA, September 25-30, 1988. Preprint Extended Abstract.

Eley BM, Garrett JR. 1983. Tissue reactions to the separate implantation of individual constituent phases of dental amalgam, including assessment by energy dispersive x-ray microanalysis. Biomaterials 4:73-80.

El-Yazigi A, Al-Saleh I, Al-Mefty O. 1984. Concentrations of Ag, Al, Au, Bi, Cd, Cu, Pb, Sb, and Se in cerebrospinal fluid of patients with cerebral neoplasms. Clin Chem 30:1358-1360.

EPA. 1977. Heavy metals in gardens near the ASARCO Smelter, Tacoma, Washington. US EPA/OTS Public Files. 40-7748027.

EPA. 1979. US Environmental Protection Agency. Federal Register 44:15926-15981.

*EPA. 1980a. Ambient water quality criteria for silver. Cincinnati, OH: US Environmental Protection Agency, Environmental Criteria and Assessment Office. PB81-117822.

*EPA. 1980b. U.S. Environmental Protection Agency. Federal Register 45:79318-79319.

EPA. 1982. Mortality in employees of the ASARCO Lead Refinery, Omaha, Nebraska with cover letter. US EPA/OTS Public Files.

*EPA. 1985a. Drinking water criteria document for silver. Cincinnati, OH: US Environmental Protection Agency, Environmental Criteria and Assessment Office. PB86-118288.

8. REFERENCES

*EPA. 1985b. Silver. Chemical, physical and biological properties of compounds present at hazardous waste sites. Washington, DC: US Environmental Protection Agency, Office of Waste Programs and Enforcement. PB89-132203.

*EPA 1986. Reference values for risk assessment. Final draft. Cincinnati, OH: US Environmental Protection Agency, Office of Solid Waste. ECAO-CIN-477

*EPA. 1987a. US Environmental Protection Agency. Code of Federal Regulations. 40 CFR 136.1.

*EPA. 1987b. US Environmental Protection Agency. Federal Register 52:21152.

*EPA. 1987c. US Environmental Protection Agency. Code of Federal Regulations. 40 CFR 116.4.

*EPA. 1987d. US Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.

EPA. 1987. US Environmental Protection Agency. Code of Federal Regulations. 40 CFR 117.3.

*EPA. 1988a. Health Advisory Draft for Silver. US Environmental Protection Agency, Office of Drinking Water, Washington, DC. (Prepublication draft).

*EPA. 1988b. US Environmental Protection Agency. Code of Federal Regulations. 40 CFR 302.4.

EPA. 1988. Drinking water criteria document for silver (final draft). Cincinnati, OH: US Environmental Protection Agency, Environmental Criteria and Assessment Office. ECAO-CIN-026.

*EPA. 1989a. Interim Methods for Development of Inhalation Reference Doses. US Environmental Protection Agency, Office of Health and Environmental Assessment. Washington, DC. EPA 600/8-88/066F.

*EPA. 1989b. US Environmental Protection Agency. Federal Register 54:22062.

Eturska M, Obreshkova E. 1979. [Argyria in the prolonged use of adsorgan]. Vutr Boles 18:121-3.

Evans WH, Read JI, Caughlin D. 1985. Quantifications of results for estimating elemental dietary intakes of lithium, rubidium, strontium, molybdenum, vanadium and silver. Analyst 110:873-877.

8. REFERENCES

Fallon ME, Horvath FJ. 1985. Preliminary assessment of contaminants in soft sediments of the Detroit River. J Great Lakes Res 11:373-378.

Farhan FM, Hibibi N, Mofidi J, et al. 1979. Direct determination of traces of heavy metals in canned vegetables by arc spectrography. J Agric Food Chem 27:637-638.

*FDA. 1988a. US Food and Drug Administration. Code of Federal Regulations. 21 CFR 103.35.

*Fisher NS, Bohe M, Teyssie J-L. 1984. Accumulation and toxicity of Cd, Zn, Ag, and Hg in four marine phytoplankters. Mar Ecol Prog Ser 18:201-213.

Flessel CP, Furst A, Radding SB. 1980. A comparison of carcinogenic metals. In: Sigel H, ed. Metal ions in biological systems. Vol. 10, New York, NY: M. Dekker, 23-54.

*Forycki Z, Zegarski W, Bardzik J, et al. 1983. Acute silver poisoning through inhalation. Bulletin of the Institute of Maritime and Tropical Medicine in Gdynia 34:199-203.

Fowler BA, Nordberg PF. 1986. Specific metals. In: Friberg L, Nordberg GF, Vouk VB, eds. Handbook on the toxicology of metals. Vol. 2, 2nd ed. New York, NY: Elsevier Science Publishing Co., Inc., 521-531.

*Fox CL, Rappole BW, Stanford W. 1969. Control of Pseudomonas infection in rats. Surg Gynecol and Obstet 128:1021-1026.

Frank R, Stonefield KI, Luyken H, et al. 1986. Survey of elemental contents in two organs of slaughtered bovine, porcine and avian specimens, Ontario, Canada 1980-83. Environmental Monitoring and Assessment 6:259-265.

Franz H. 1968. [Demonstration of small amounts of tissue-bound silver]. Histochemie 12:227-229.

*Freeman RA. 1979. Ecological kinetics of silver in an alpine lake ecosystem. In: Marking LL, Kimerle RA, eds. Aquatic toxicology. Philadelphia, PA: American Society for Testing and Materials, 342-358.

Frei JV, Stephens P. 1968. The correlation of promotion of tumor growth and of induction of hyperplasia in epidermal two-stage carcinogenesis. Br J Cancer 22:83-92.

Fujita S. 1971. Silver-palladium-gold alloys carcinogenicity and acid mucopolysacharides in the induced tumors. Chem Abstracts 77:136075a.

8. REFERENCES

*Furchner JE, Richmond CR, Drake GA. 1968. Comparative metabolism of radionuclides in mammals-IV. Retention of silver-110m in the mouse, rat, monkey, and dog. Health Physics 15:505-514.

Furst A. 1981. Bioassay of metals for carcinogenesis: Whole animals. Environ Health Perspect 40:83-91.

Furst A, Schlauder MC. 1977. Inactivity of two noble metals as carcinogens. J Environ Pathol Toxicol 1:51-57.

Galloway JN, Likens GE. 1979. Atmospheric enhancement of metal deposition in Adirondack lake sediments. Limnology Oceanography 24:427-433.

Gallyas F. 1979. Factors affecting the formation of metallic silver and the binding of silver ions by tissue components. Histochemistry 64:97-109.

Gammill JC, Wheeler B, Carothers EL, et al. 1950. Distribution of radioactive silver colloids in tissues of rodents following injection by various routes. Proc Soc Exp Biol Med 74:691-695.

Ganther HE. 1980. Interactions of vitamin E and selenium with mercury and silver. Ann NY Acad Sci 355:212-226.

Ganther HE, Wagner PA, Sunde ML, et al. 1973. Protective effects of selenium against heavy metal toxicities. Proc Univ MO Annu Conf Trace Subst Environ Health. 7:247-252.

*Gaul LE, Staud AH. 1935. Clinical spectroscopy. Seventy cases of generalized argyrosis following organic and colloidal silver medication, including a biospectrometric analysis. J Am Med Assoc 104:1387-1390.

George SG, Pirie BJS, Calabrese A, et al. 1986. Biochemical and ultrastructural observations of long-term silver accumulation in the mussel, Mytilus edulis. Marine Environmental Research 18:255-265.

Gerritse RG, Vriesema R, Dalenberg JW, et al. 1982. Effect of sewage sludge on trace element mobility in soils. J Environ Qual 11:359-364.

Gjerdet NR, Kallus T, Hensten-Pettersen A. 1987. Tissue reactions to implanted orthodontic wires in rabbits. Acta Odontol Scand 45:163-169.

Goebel HH, Muller J. 1973. Ultrastructural observations on silver deposition in the choroid plexus of a patient with argyria. Acta Neuropathol (Berl) 26:247-251.

Goff H, Powers EL. 1975. Effects of X-rays on Ag-DNA complexes. Int J Radiat Biol 27:503-507.

8. REFERENCES

Goldberg ED. 1986. The mussel watch concept. Environmental Monitoring and Assessment 7:91-103.

Goldberg RL, Kaplan SR, Fuller GC. 1983. Effect of heavy metals on human rheumatoid synovial cell proliferation and collagen synthesis. Biochem Pharmacol 32:2763-2766.

Goldschmidt PR, Cogen RB, Taubman SB. 1976. Effects of amalgam corrosion products on human cells. J Periodontal Res 11:108-115.

Goodman Gilman A, Goodman LS, Rall TW, et al., ed. 1985. Goodman and Gilman's the pharmacological basis of therapeutics. New York, NY: Macmillan Publishing Company, 951; 966-967; 1107.

Gould GW, Colyer J, East JM, et al. 1987. Silver ions trigger Ca2+ release by interaction with the (Ca2+-Mg2+)-ATPase. J Biol Chem 262:7676-7679.

Grabowski BF, Haney WG Jr. 1972. Characterization of silver deposits in tissue resulting from dermal application of a silver-containing pharmaceutical. J Pharm Sci 61:1488-1490.

Granati A, Lenzi R, Poggini G, et al. 1982. [Evaluation of the impact of silver on human health]. Difesa Sociale 61:90-112. (Italian).

*Grasso P, Abraham R, Hendy R, et al. 1969. The role of dietary silver in the production of liver necrosis in vitamin E-deficient rats. Exp Mol Pathol 11:186-199.

Grasso P, Abraham R, Hendy R, et al. 1973. Hepatocellular necrosis from dietary silver in vitamin E-deficient rats [Abstract]. J Pathol 100:ix.

*Grayson M, ed. 1978. Silver and silver alloys; Silver and compounds. Kirk-Othmer encyclopedia of chemical technology. Vol. 21, 3rd ed. 1-32.

Green B. 1967. Effects of silver ions on deoxyribonucleic acid-polycyclic hydrocarbon complexes. Biochem J 104:63-64.

Greenberg RR, Zoller WH, Gordon GE. 1978. Composition and size distributions of particles released in refuse incineration. Environ Sci Technol 12:566-573.

Greene RM, Su WPD. 1987. Argyria. American Family Physician 36:151-154.

Gregus Z, Klaassen CD. 1986. Disposition of metals in rats: A comparative study of fecal, urinary, and biliary excretion and tissue distribution of eighteen metals. Toxicol Appl Pharmacol 85:24-38.

8. REFERENCES

Greig RA, Wenzloff DR, Adams A, et al. 1977. Trace metals in organisms from ocean disposal sites of the middle eastern United States. Arch Environ Contam Toxicol 6:395-409.

Greig RA, Schurman S, Pereira J, et al. 1983. Metals and PCB concentrations in Windowpane Flounder from Long Island Sound. Bull Environ Contam Toxicol 31:257-262.

Habu T. 1968. Histopathological effects of silver-palladium-gold alloy implantation on the oral submucous membranes and other organs [Abstract]. Shika Igaku 31:17-48.

*Ham KN, Tange JD. 1972. Silver deposition in rat glomerular basement membrane. Aust J Exp Bio Med Sci 50:423-434.

Hamilton A, Hardy HL. 1974. Silver. Industrial toxicology. 3rd ed. Acton, MA: Publishing Sciences Group, Inc., 171-172.

Hamilton EI, Minski MJ. 1972/1973. Abundance of the chemical elements in man's diet and possible relations with environmental factors. Sci Total Environ 1:375-394.

Hamilton EI, Minski MJ, Cleary JJ. 1972/1973. The concentrations and distribution of some stable elements in healthy tissues from the United Kingdom. An environmental study. Sci Total Environ 1:341-374.

Hanna C, Fraunfelder FT, Sanchez J. 1974. Ultrastructural study of the cornea and conjunctiva. Arch Ophthalmol 92:18-22.

Hanzlik PJ, Presho E. 1923. Comparative toxicity of metallic lead and other heavy metals for pigeons. J Pharmacol Exp Ther 21:145-150.

Harding HE. 1951. Fibrosis in the lungs of a silver finisher. Br J Ind Med 8:256-263.

Harker JM, Hunter D. 1935. Occupational argyria. Br J Dermatol Syph 47:441-455.

*Harrison PR, Rahn KA, Dams R, et al. 1971. Areawide trace metal concentrations measured by multielement neutron activation analysis. Journal of the Air Pollution Control Association 21:563-570.

Harvey RW, Luoma SN. 1985. Effect of adherent bacteria and bacterial extracellular polymers upon assimilation by Macoma balthica of sediment-bound cadmium, zinc and silver. Mar Ecol Prog Ser 22:281-289.

8. REFERENCES

Hauser TR, Bromberg SM. 1982. EPA's monitoring program at Love Canal 1980. Environmental Monitoring and Assessment 2:249-272.

Heit M. 1979. Variability of the concentrations of seventeen trace elements in the muscle and liver of a single striped bass, Marone saxatilis. Bull Environ Contam Toxicol 23:1-5.

Heit M, Tan Y, Klusek C, et al. 1981. Anthropogenic trace elements and polycyclic aromatic hydrocarbon levels in sediment cores from two lakes in the Adirondack acid lake region. Water Air Soil Pollut 15:441-464.

*Hem JD. 1970. Study and interpretation of the chemical characteristics of natural waters. US Geological Survey Paper 1473. Washington, DC: US Geological Service., 202-203.

Henry SA. 1950. Cutaneous cancer in relation to occupation. Annals of the Royal College of Surgeons of England 7:425-454.

Henry WM, Knapp KT. 1980. Compound forms of fossil fuel fly ash emissions. Environmental Science and Technology 14:450-456.

Hershelman GP, Schafer HA, Jan T-K, et al. 1981. Metals in marine sediments near a large California municipal outfall. Marine Pollution Bulletin 12:131-134.

*Heyl T. 1979. Contact dermatitis from silver coat. Contact Dermatitis 5:197.

Hildebrand SG, Cushman RM, Carter JA. 1976. The potential toxicity and bioaccumulation in aquatic systems of trace elements present in aqueous coal conversion effluents. Proc Univ MO Annu Conf Trace Subst Environ Health. 10:305-313.

*Hill WR, Pillsbury DM. 1939. Argyria, the pharmacology of silver. Baltimore, MD: The Williams and Wilkins Co.

Hill CH, Matrone G. 1970. Chemical parameters in the study of in vivo and in vitro interactions of transition elements. Fed Proc 29:1474-1481.

Hirakawa K. 1983. Determination of silver and cerium in the liver and the kidney from a severely burned infant treated with silver sulfadiazine and cerium nitrate. Radioisotopes 32:59-65. (Japanese).

Hodge VF, Folson TR. 1972. Estimate of the world budget of fallout silver nuclides. Nature 237:98-99.

8. REFERENCES

Hoekstra WG. 1975. Biochemical function of selenium and its relation to vitamin E. Fed Proc 34:2083-2089.

*Hoey MJ. 1966. The effects of metallic salts on the histology and functioning of the rat testis. J Reprod Fertil 12:461-471.

*Holland MK, White IG. 1980. Heavy metals and spermatozoa. 1. Inhibition of the motility and metabolism of spermatozoa by metals related to copper. Fertil Steril 34:483-489.

Holland MK, Suter DAI, White IG. 1976. Possible mechanisms involved in the reduction in motility of human spermatozoa by copper zinc and silver. J Reprod Fertil 46:507-508.

Housley M, Heckingbottom R, Todd CJ. 1977. The interaction of Ag with Si(III). Surface Science 68:179-188.

*Howlett C, Taylor A. 1978. Measurement of silver in blood by atomic-absorption spectrophotometry using the micro-cup technique. Analyst 103:916-920.

*HSDB. 1988. Hazardous Substances Databank. National Library of Medicine, National Toxicology Information Program, Bethesda, MD. December 5, 1988.

Hudson E. 1970. A survey of silver recovery. Part I. The mechanics of silver recovery. Radiography 36:263-269.

Huff B, ed. 1988. Physicians desk reference. 42nd ed. Oradell, NJ: Medical Economics Co., 122, 409, 416, 961.

Huggins HA. 1983. Mercury--a factor in mental disease? Part 1. Can mercury-silver amalgams cause psychiatric symptoms. Oral Health 73:42-45.

*Hung S-C, Qu C-L, Wu S-S. 1982. Spectrophotometric determination of silver with 2-(3,5-dibromo-2-pyridylazo)-5-diethylaminophenol in the presence of anionic surfactant. Talanta 29:85-88.

Hunt JS, McGiven AR, Day WA. 1976. Immune complex glomerular disease in argyric mice. Pathology 8:205-210.

Hunter D. 1983. Silver and compounds. In: Parmeggiani L, ed. Encyclopaedia of occupational health and safety. Vol. 2, 3rd ed. Geneva: International Labour Office, 2047-2048.

Indraprasit S, Alexander GV, Gonick HC. 1974. Tissue composition of major and trace elements in uremia and hypertension. J Chronic Dis 27:135-161.

8. REFERENCES

Ireland MP. 1988. A comparative study of the uptake and distribution of silver in a slug, Arion water and a snail, Achatina fulica. Comp Biochem Physiol 90C:189-194.

*IRIS. 1989. Integrated Risk Information System. US Environmental Protection Agency, Cincinnati, OH.

*Iyengar GV, Tanner JT, Wolf WR, et al. 1987. Preparation of a mixed human diet material for the determination of nutrient elements, selected toxic elements and organic nutrients: A preliminary report. Sci Total Environ 235-252.

Jensen LS. 1975. Modification of a selenium toxicity in chicks by dietary silver and copper. J Nutr 105:769-775.

Jensen LS, Peterson RP, Falen L. 1974. Inducement of enlarged hearts and muscular dystrophy in turkey poults with dietary silver. Poultry Science 53:57-64.

John W, Kaifer R, Rahn K, et al. 1973. Trace element concentrations in aerosols from the San Francisco Bay area. Atmospheric Environment 7:107-118.

*Johnson CA. 1976. The determination of some toxic metals in human liver as a guide to normal levels in New Zealand. Part I. Determination of Bi, Cd, Cr, Co, Cu, Pb, Mn, Ni, Ag, Ti and Zn. Analytica Chemica Acta 81:69-74.

Johnson JS, Kilburn KH. 1983. Cadmium induced metal fume fever: Results of inhalation challenge. Am J Ind Med 4:533-540.

*Jones AM, Bailey JA. 1974. Effect of silver from cloud seeding on cecal flora of rabbits. Water Air Soil Pollut 3:353-363.

Jones CJ, McGugan PJ, Lawrence PF. 1978. An investigation of the degradation of some dry cell batteries under domestic waste landfill conditions. Journal of Hazardous Material 2:259-290.

Just J, Szniolis A. 1938. Germicidal properties of silver in water. Journal American Water Works Association 28:492-506.

*Kaczmar SW, D'Itri FM, Zabik MJ. 1984. Volatilization rates of selected haloforms from aqueous environments. Environmental Toxicology and Chemistry 3:31-35.

Kalistratova VS, Kogan AG, Kozlova MD. 1966. [Behavior of 111Ag in animals]. In: Moskalev I, ed. Raspredel Biol Deistria Radioacktiv Izotop, Sb Statei. Moscow, Russia: Atomizdat, 146-151. (Russian).

8. REFERENCES

Kallus T, Hensten-Pettersen A, Mjor I A. 1983. Tissue response to allergenic leachables from dental material. J Biomed Mater Res 17:741-755.

*Kanematsu N, Hara M, Kada T. 1980. Rec assay and mutagenicity studies on metal compounds. Mutation Research 77:109-116.

Kargov SI, Korolev NI, Stanislavskii OB, et al. 1986. [Interaction of immobilized DNA with silver ions]. Mol Biol (Mosk) 20:1499-1505. (Russian).

Kehoe JC. 1984. Intracanal corrosion of a silver cone producing a localized argyria: Scanning electron microscope and energy dispersive x-ray analyzer analyses. Journal of Endodontics 10:199-201.

*Kehoe RA, Cholak J, Story RV. 1940. A spectrochemical study of the normal ranges of concentrations of certain trace metals in biological materials. J Nutr 19:579-592.

Kempton S, Sterritt RM, Lester JN. 1987. Heavy metal removal in primary sedimentation. I. The influence of metal solubility. Sci Total Environ 63:231-247.

Kempton S, Sterritt RM, Lester JN. 1987. Heavy metal removal in primary sedimentation II. The influence of metal speciation and particle size distribution. Sci Total Environ 63:247-258.

Kent NL, McCance RA. 1941. The absorption and excretion of 'minor' elements by man. I. Silver, gold, lithium, boron and vanadium. Biochemical Journal 35:837-844.

Kesseru E, Leon F. 1974. Effect of different solid metals and metallic pairs on human sperm motility. Int J Fertil 19:81-84.

Kesseru E, Hurtado H, Muhe B. 1974. Copper IUD: Enhancement of its efficacy by the addition of silver and nickel. Contraception 9:141-151.

Kettner VW, Vogel K, Kruger G. 1970. Contribution to the clinical picture of argyrosis. Deut Gesundheitsw 25:1746-1747.

Kharchenko PD, Stepanenko PZ. 1972. [Peculiarities of disturbances of albino rat higher nervous activity during the action of silver electrolytic solutions]. Fiziol Zh (Kiev) 18:596-600. (Ukranian).

Kharchenko PD, Berdyshev GD, Stepanenko PZ, et al. 1973. [Change in the nucleic acid level in rat brain and liver during long-term introduction of silver ions in drinking water]. Fiziol Zh (Kiev) 19:362-368. (Ukranian).

8. REFERENCES

*Kharkar DP, Turekian KK, Bertine KK. 1968. Stream supply of dissolved silver, molybdenum, antimony, selenium, chromium, cobalt, rubidium and cesium to the oceans. Geochimica et Cosmochimica Acta 32:285-298.

King JS. 1966. A comparative investigation of neuroglia in representative vertebrates: A silver carbonate study. J Morphol 119:435-465.

Klaassen CD. 1978. Effect of metallothionein on hepatic disposition of metals. Am J Physiol 234:E47-E53.

*Klaassen CD. 1979a. Effect of spironolactone on the biliary excretion and distribution of metals. Toxicol Appl Pharmacol 50:41-48.

*Klaassen CD. 1979b. Biliary excretion of silver in the rat, rabbit and dog. Toxicol Appl Pharmacol 50:49-56.

*Klein DH. 1972. Mercury and other metals in urban soils. Environmental Science and Technology 6:560-562.

Klein DH, Russell P. 1973. Heavy metals: Fallout around a power plant. Environmental Science and Technology 7:357-358.

*Klusek CS, Miller KM, Heit M. 1983. Trace element and radionuclide mass balances at a coal-fired electric generating station. Environ Int 9:139-144.

Kober GM. 1916. The gold, silver, jewelry and allied industries. In: Kober GM, Hanson WC, eds. Diseases of occupation and vocational hygiene. Philadelphia, PA: P. Blakiston's Son and Co., 580-585.

Kojo T, Kaneko T, Ito A, et al. 1986. [Experimental studies of the effect of metal cores (silver alloy) on the gingival tissue. 2nd report. Extensive investigation of gingival discoloration]. J Jpn Prosthoclort Soc 30:1278-1286. (Japanese).

Kone BC, Kaleta M, Gullans SR. 1988. Silver ion (Ag+)-induced increases in cell membrane potassium and sodium permeability in the renal proximal tubule: Reversal by thiol reagents. J Membr Biol 102:11-19.

Konga M, Nakamura T, Jyoyama T, et al. 1982. Industrial hygienic approach to the workers exposed to inorganic silver. Proceedings of the tenth Asian conference on occupational health, 2:584-587. September 5-10, Singapore.

*Konradova V. 1968. The ultrastructure of the tracheal epithelium in rabbits following inhalation of aerosols of colloidal solutions of heavy metals. II. Signs of cell alteration in the epithelium after 8 hour inhalation of colloidal solutions of iron and silver. Folia Morphol (Praha) 16:265-271.

8. REFERENCES

Konradova V. 1968. The ultrastructure of the tracheal epithelium in rabbits following the inhalation of aerosols of colloidal solutions of heavy metals. 1. Changes in the ultrastructure of the tracheal epithelium after 2-hour inhalation of colloidal solutions of iron and silver. Folia Morphol (Praha) 16:258-264.

*Kopp JF. 1969. The occurrence of trace elements in water. Proc Univ MO Annu Conf Trace Subst Environ Health. 3:59-73.

Kopp JF, Kroner RC. 1967. Tracing water pollution with an emission spectrograph. J Water Pollut Cont Fed 39:1659-1668.

Kosarek LJ. 1981. Removal of various toxic heavy metals and cyanide from water by membrane processes. In: Cooper WJ, ed. Chemistry in water reuse. Vol. 1, Ann Arbor, MI: Ann Arbor Science Publishers, Inc., 261-280.

Krebs A. 1983. [Drug induced nail disorders]. Deutsch Apotheker Zeitung 123:557-561. (German).

Kroner RC, Kopp JF. 1965. Trace elements in six water systems of the United States. Journal American Water Works Association 57:150-156.

Kulskii LA, Kharchenko PD, Stepanenko PZ. 1972. [Dynamics of cortical activity changes in albino rats after chronic silver intoxication]. Dopov Akad Nauk Ukr RSR Ser B 34:660-662. (Ukranian).

*Landas S, Fischer J, Wilkin LD, et al. 1985. Demonstration of regional blood-brain barrier permeability in human brain. Neurosci Lett 57:251-256.

Larsen PF, Zdanowicz V, Johnson AC. 1983. Trace metal distribution in the surficial sediments of Penobscat Bay, Maine. Bull Environ Contam Toxicol 31:566-573.

La Torraca F. 1962. [Anatomic, histopathological, and histochemical aspects of acute experimental intoxication with silver salts]. Folia Medica 45:1065-1069. (Italian).

*Law SL, Gordon GE. 1979. Sources of metals in municipal incinerator emissions. Environmental Science and Technology 13:432-438.

Lee RE Jr, Von Lehmden DJ. 1973. Trace metal pollution in the environment. Journal of the Air Pollution Control Association 23:853-857.

Leirskar J. 1974. On the mechanism of cytotoxicity of silver and copper amalgams in a cell culture system. Scand J Dent Res 82:74-81.

8. REFERENCES

Leirskar J, Heigeland K. 1972. A methodologic study of the effect of dental materials on growth and adhesion of animal cells in-vitro. Scand J Dent Res 80:120-133.

Leirskar J, Helgeland K. 1981. Mechanism of toxicity of dental materials. International Endodontic Journal 14:42-48.

Lemez L. 1980. Sites for experimental production of tracheal and/or oesophageal malformations in 4-day-old chick embryos. Folia Morphol (Praha) 28:52-55.

Leroux-Robert C, Benevent J, Benevent D, et al. 1982. [Renal argyria discovered in nephrotic syndrome]. Nephrologie 3:101. (French).

Lester JN. 1983. Significance and behavior of heavy metals in waste water treatment processes 1. Sewage treatment and effluent discharge. Sci Total Environ 30:1-44.

*Lester JN, Sterritt RM, Kirk PWW. 1983. Significance and behavior of heavy metals in waste water treatment processes II. Sludge treatment and disposal. Sci Total Environ 30:45-83.

*Letkiewicz F, Spooner C, Macaluso C, et al. 1984. Occurrence of silver in drinking water, food, and air. Report to US Environmental Protection Agency, Office of Drinking Water, Criteria and Standards Division, Washington, DC, by JRB Associates, McLean, VA.

Lindh U, Brune D, Nordberg G, et al. 1980. Levels of antimony, arsenic, cadmium, copper, lead, mercury, selenium, silver, tin and zinc in bone tissue of industrially exposed workers. Sci Total Environ 16:109-116.

*Lindsay WL, Sadiq M. 1979. Theoretical solubility relationships of silver in soils. In: Klein DA, ed. Environmental impacts of artificial ice nucleating agents. Dowden, Hutchinson, and Ross, Inc.

Lockhart SP, Rushworth A, Azmy AAF, et al. 1983. Topical silver sulphadiazine: Side effects and urinary excretion. Burns 10:9-12.

*Loeb LA, Sirover MA, Weymouth LA, et al. 1977. Infidelity of DNA synthesis as related to mutagenesis and carcinogenesis. J Toxicol Environ Health 2:1297-1304.

*Loeffler KU, Lee WR. 1987. Argyrosis of the lacrimal sac. Graefe's Arch Clin Exp Ophthalmol 225:146-150.

8. REFERENCES

Luis AS, Duarte CS. 1960. Experimental study on the pathogenesis of acute pulmonary edema. I. Pulmonary edema induced by silver nitrate [Abstract]. Mal Cardiovasc 56:39-49.

*Luk KFS, Maki AH, Hoover RJ. 1975. Studies of heavy metal binding with polynucleotides using optical detection. J Am Chem Soc 97:1241-1242.

Lukanov J, Atmadjov P. 1979. Investigating the effect of silver ions on the contractile function of smooth-muscle preparations from guinea pig stomach, in vitro. Folia Med (Plovdiv) 21:11-19.

Luoma SN, Jenne EA. 1977. The availability of sediment-bound cobalt, silver and zinc to a deposit-feeding clam. In: Drucker H, Wilding RE, eds. Biological implications of metals in the environment. Springfield, VA: National Technical Information Service.

Lyons WMB, Fitzgerald WMF. 1980. Trace metal fluxes to nearshore Long Island Sound sediments. Mar Pollut Bull 11:157-161.

Lytle PE. 1984. Fate and speciation of silver in publicly owned treatment works. Environmental Toxicology and Chemistry 3:21-30.

MacIntyre EH, McClatchy JK, Rudolph H, et al. 1973. Identification of silver in a periapical lesion of a tooth. Am J Clin Pathol 60:613-615.

*MacIntyre D, McLay ALC, East BW, et al. 1978. Silver poisoning associated with an antismoking lozenge. Br Med J 2:1749-1750.

Mackison FW, Stricoff RS, Partridge LJ Jr. 1980. Pocket guidelines to chemical hazards. Washington, DC: US Government Printing Office, 1661.

Magos L, Webb M. 1978. Theoretical and practical considerations on the problem of metal-metal interaction. Environ Health Perspect 25:151-154.

*Malcolm R, Currey HS, Mitchell MA, et al. 1986. Silver acetate gum as a deterrent to smoking. Chest 90:107-111.

Malins DC, McCain BB, Brown DW, et al. Chemical pollutants in sediments and diseases of bottom-dwelling fish in Puget Sound, Washington. Environmental Science and Technology 18:705-713.

Mangal PC, Verma KB. 1979. Effect of induced skin cancer on the concentration of some trace elements. Indian J Med Res 69:290-295.

Marie J, Leveque B, Watchi JM, et al. 1966. [Argyria in a child following pharyngeal spracy of silver salts repeated for 6 years]. Ann Pediatr 13:2657-2659. (French).

8. REFERENCES

Marino AA, Berger TJ, Becker RO, et al. 1974. The effect of selected metals on marrow cells in culture. Chem Biol Interact 9:217-223.

*Marks R. 1966. Contact dermatitis due to silver. Br J Dermatol 78:606-607.

*Marshall JP II, Schneider RP. 1977. Systemic argyria: Secondary to topical silver nitrate. Arch Dermatol 113:1077-1079.

Martin M, Castle W. 1984. Petrowatch: Petroleum hydrocarbons, synthetic organic compounds and heavy metals in mussels from the Monterey Bay area of central California. Marine Pollution Bulletin 15:259-266.

Masiak M, Owczarek H, Skowron S, et al. 1982. Serum levels of certain trace elements (Ag, Co, Cr) in healthy subjects (part II). Acta Physiol Pol 33:65-73.

Maslenko AA. 1976. [Effects of "silver water" and drinking water treated with silver on the digestive organs]. Vrach Delo, Issue 5, 88-90. (Russian).

*Massa V. 1969. [Analysis of silver, in the presence of other metals, by means of dithizonate chromatography and photodensitometry. Drug control applications]. Trav Soc Pharm Montpellier 29:221-224. (French).

Matuk Y. 1983. Distribution of radioactive silver in the subcellular fractions of various tissues of the rat and its binding to low molecular weight proteins. Can J Physiol Pharmacol 61:1391-1395.

*Matuk Y, Ghosh M, McCulloch C. 1981. Distribution of silver in the eyes and plasma proteins of the albino rat. Can J Ophthalmol 16:145-150.

*Mauss Y, Poulet P, Steibel J, et al. 1980. Interaction of proflavine-calf thymus DNA complexes with Ag+ and Hg++ ions. Studia Biophysica 81:95-96.

McCabe LJ, Symons JM, Lee RD, et al. 1970. A survey of community water supply systems. Journal of the American Water Works Association 62:670-687.

*McCoy EC, Rosenkranz HS. 1978. Silver sulfadiazine: Lack of mutagenic activity. Chemotherapy (Basel) 24:87-91.

McDermot DJ, Alexander GV, Young DR, et al. 1976. Metal contamination of flatfish around a large submarine outfall. Journal of the Water Pollution Control Federation 48:1913-1918.

McDowell LR, Forseth JA, Piper RC. 1978. Influence of arsenic, sulfur, cadmium, tellurium, silver and selenium on the selenium-vitamin E deficiency in the pig. Nutrition Reports International 17:19-34.

8. REFERENCES

McGinnis JP Jr, Greer JL, Daniels DS. 1985. Amalgam tattoo: Report of an unusual clinical presentation and the use of energy dispersive x-ray analysis as an aid to diagnosis. J Am Dent Assoc 110:52-54.

McLaughlin AIG, Grout JLA, Barrie HJ, et al. 1945. Iron oxide dust and the lungs of silver finishers. Lancet, March 17, 337-341.

*McMahon JT, Bergfeld WF. 1983. Metallic cutaneous contaminant mimicking malignant melanoma. Cleveland Clinic Quarterly 50:177-181.

Mehregan AH, Faghri B. 1974. Implantation dermatoses. Acta Dermatovener (Stockholm) 54:61-64.

*Mehta AC, Dawson-Butterworth K, Woodhouse MA. 1966. Argyria. Electron microscopic study of a case. Br J Dermatol 78:175-179.

Mertz DP, Koschnick R, Wilk G, et al. 1968. [Studies on the metabolism of trace elements in humans. I. Serum values for cobalt, nickel, silver, cadmium, chromium, molybdenum, manganese]. Z Klin Chem Klin Biochem 6:171-174. (German).

Mertz DP, Wilk G, Koschnick R. 1975. [Conditions affecting renal excretion of silver by humans. Studies on metabolism of trace elements. VIII]. Z Klin Chem Klin Biochem 13:13-15. (German).

Minoia C, Oppezzo MC, Pozzoli L, et al. 1985. [Environmental and biological monitoring of subjects occupationally exposed]. G Ital Med Lav 7:65-73. (Italian).

*Mitteldorf AJ, Landon DO. 1952. Spectrochemical determination of the mineral-element content of beef. Analytical Chemistry 24:469-472.

*Moffat DB, Creasey M. 1972. The distribution of ingested silver in the kidney of the rat and of the rabbit. Acta Anat 83:346-355.

Mogilnicka EM, Piotrowski JK, Tomaszewski A. 1976. Effect of some metals (Rb, Cs, Ag, Ti, Sb, U) on metallothionein level in the liver and kidney of the rat. Bromat Chem Toksykol 9:357-359. (Polish)

Mogilnicka EM, Milaszewicz M, Piotrowsk JK. 1978. [Binding of silver in the liver of the rat]. Bromat Chem Toksykol 11:59-65. (Polish).

Moller B. 1979. Reactions of human dental pulp to silver amalgam restorations. A study with emphasis on source material characteristics. Swedish Dent [Suppl] 2:1-37.

8. REFERENCES

Moore JW, Sutherland DJ. 1981. Distribution of heavy metals and radionuclides in sediments, water, and fish in an area of Great Bear Lake contaminated with mine wastes. Arch Environ Contam Toxicol 10:329-338.

Morgan WKC. 1984. Other pneumoconioses. In: Morgan WKC, Seaton A, eds. Occupational lung disease. 2nd ed. Philadelphia, PA: W.B. Saunder Company, 449-497.

*Moss AP, Sugar A, Hargett NA, et al. 1979. The ocular manifestations and functional effects of occupational argyrosis. Arch Ophthalmol 97:906-908.

Muroma A. 1961. Skin reactions produced by certain metallic salts. Annales Medicine Experimentalis et Biologiae Fenniae 39:277-279.

*Murthy GK, Rhea U. 1968. Cadmium and silver content of market milk. J Dairy Science 51:610-613.

*Nadkarni RA, Ehmann WD, Burdick D. 1970. Investigations on the relative transference of trace elements from tobacco into smoke condensate. Tobacco 170:25-27.

Naganuma A, Tanaka T, Maeda K, et al. 1983. The interaction of selenium with various metals in vitro and in vivo. Toxicology 29:77-86.

Nakamuro K, Sayato Y. 1986. Studies on the toxicity of silver ion in water filtered through a household water purifier equipped with a silver-coated charcoal filter. Eisei Kagaku 32:28-33.

*Nakashima R, Sasaki S, Shibata S. 1975. Determination of silver in biological materials by high-frequency plasma-torch emission spectrometry. Analytica Chimica Acta 77:65-70.

*NAS/NRC. 1989. Biological markers in reproductive toxicology. National Research Council. Board of Environmental Studies and Toxicology. Committee on Biological Markers. 15-35.

Nathanson JA, Bloom FE. 1976. Heavy metals and adenosine cyclic 3',5'-monophosphate metabolism: Possible relevance to heavy metal toxicity. Mol Pharmacol 12:390-398.

Nechay BR, Saunders JP. 1984. Inhibition of adenosine triphosphates in vitro by silver nitrate and silver sulfadiazine. Journal of the American College of Toxicology 3:37-42.

Nehring RB. 1976. Aquatic insects as biological monitors of heavy metal pollution. Bull Environ Contam Toxicol 15:147-154.

8. REFERENCES

Neri LC, Hewitt D, Schreiber GB, et al. 1975. Health aspects of hard and soft waters. Journal American Water Works Association 67:403-409.

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

Nilner K, Glantz P-O. 1982. The prevalence of copper-, silver-, tin-, and zinc-ions in human saliva. Swed Dent J 6:71-77.

*NIOSH. 1976. National Occupational Hazard Survey (1970) Database. US Department of Health and Human Services, National Institute for Occupational Safety and Health, Cincinnati, OH

*NIOSH. 1984a. National Occupational Exposure Survey (1980-1983) Database. US Department of Health and Human Services, National Institute for Occupational Safety and Health, Cincinnati, OH.

*NIOSH. 1984b. NIOSH, manual of analytical methods. Washington, DC: US Government Printing Office., 73001-73005.

*NIOSH. 1985. Pocket guide to chemical hazards. Washington, DC: US Department of Health and Human Services. DHEW (NIOSH) Publication No 78-210.

Nishimura M. 1978. [A study on the cytotoxicity of Au-Pd-Ag alloys containing Cd (in vitro)]. Shika Rikogaku Zasshi 19:1-7. (Japanese).

*Nishioka H. 1975. Mutagenic activities of metal compounds in bacteria. Mutat Res 31:185-189.

Nordberg GF, Gerhardsson L. 1988. Silver. In: Seiler HG, Sigel H, eds. Handbook on toxicity of inorganic compounds. New York, NY: Marcel Dekker, Inc., 619-624.

Norden B, Matsuoka Y, Kurucsev T. 1986. Nucleic acid-metal interactions: V. The effect of silver(I) on the structures of A- and B-DNA forms. Biopolymers 25:1531-1545.

Nriagu JR. 1979. Global inventory of natural and anthropogenic emissions of trace metals to the atmosphere. Nature 279:409-411.

*NRC. 1977. Silver. In: Drinking water and health. Vol. 2. Washington, DC: National Academy of Sciences, National Research Council, 102-106.

*Nuttall KL. 1987. A model for metal selenide formation under biological conditions. Med Hypotheses 24:217-221.

8. REFERENCES

Oh SH, Whanger PD, Deagen JT. 1981. Tissue metallothionein: Dietary interaction of cadmium and zinc with copper, mercury, and silver. J Toxicol Environ Health 7:547-560.

OHM, TADS. 1988. Oil and Hazardous Materials Technical Assistance Data System. Chemical Information System (CIS). December 5, 1988.

*Okazaki RK, Panietz MH. 1981. Depuration of twelve trace metals in tissues of the oysters Crassostrea gigas and Crassostrea virginica. Marine Biology 63:113-120.

*Olcott CT. 1947. Experimental argyrosis. III. Pigmentation of the eyes of rats following ingestion of silver during long periods of time. Am J Pathol 23:783-789.

*Olcott CT. 1948. Experimental argyrosis. IV. Morphologic changes in the experimental animal. Am J Path 24:813-833.

*Olcott CT. 1950. Experimental argyrosis. V. Hypertrophy of the left ventricle of the heart. Archives of Pathology 49:138-149.

Olson BH, Guinn VP. 1978. Accumulations of trace elements in soil and plants from land disposal of secondary domestic wastewater. In: Land treatment of wastewater international symposium, Hanover, NH. 2:289-299

Oppenheimer BS, Oppenheimer ET, Danishefsky I, et al. 1956. Carcinogenic effect of metals in rodents. Cancer Res 16:439-441.

Orentreich N, Pearlstein HH. 1969. Traumatic tattoo due to silver salt. Arch Dermatol 100:107-108.

Orstavik D, Hongslo JK. 1985. Mutagenicity of endodontic sealers. Biomaterials 6:129-132.

Osborn JF, Santhanam S, Davidson CI, et al. 1984. Characterization of airborne trace metal and trace organic species from coal gasification. Environmental Monitoring and Assessment 4:317-333.

*OSHA. 1988a. US Department of Labor, Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.20

*OSHA. 1988b. US Department of Labor, Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1000

Owens CJ, Yarbrough DR III, Brackett NC. 1974. Nephrotic syndrome following topically applied sulfadiazine silver therapy. Arch Intern Med 134:332-335.

8. REFERENCES

Page AL. 1974. Fate and effects of trace elements in sewage sludge when applied to agricultural lands. A literature review study. Ultimate Disposal Research Program. Cincinnati, OH: US Environmental Protection Agency, Office of Research and Development. NTIS PB-231 171.

Palmer GR, Weine FS, Palmer MJ, et al. 1979. A study of the tissue reaction to silver cones and Ti-6Al-4V in the rhesus monkey. Journal of Endodontics 5:116-120.

*Pariser RJ. 1978. Generalized argyria: Clinicopathologic features and histochemical studies. Arch Dermatol 114:373-377.

Parkki MG. 1981. Inhibition of rat hepatic microsomal epoxide hydrase by heavy- and organometals in vitro. Adv Exp Med Biol 136:729-738. Part A.

Perry KMA. 1947. Diseases of the lung resulting from occupational dusts other than silica. Thorax 2:91-120.

*Pesch G, Reynolds B, Rogerson P. 1977. Trace metals in scallops from within and around two ocean disposal sites. Marine Pollution Bulletin 8:224-228.

Petering HG. 1976. Pharmacology and toxicology of heavy metals: Silver. Pharmacol Ther 1:127-130. Part A.

Peterson RP, Jensen LS, Harrison PC. 1973. Effect of silver-induced enlarged hearts during the first four weeks of life on subsequent performance of turkeys. Avian Diseases 17:802-806.

Pezzarossa E, Alinovi A, Ferrari C. 1983. Generalized argyria. J Cutan Pathol 10:361-363.

Pfitzer EA. 1975. Toxicology. In: Cralley LV, Atkins PR, eds. Industrial environmental health. The worker and the community. New York, NY: Academic Press, 67-128.

*Phalen RF, Morrow PE. 1973. Experimental inhalation of metallic silver. Health Phys 24:509-518.

*Pickston L, Lewin JF, Drysdale JM, et al. 1983. Determination of potentially toxic metals in human livers in New Zealand. J Anal Toxicol 7:2-6.

*Pierce FD, Gortatowski MJ, Mecham HD, et al. 1975. Improved automated extraction method for atomic adsorption spectrometry. Analytical Chemistry 47:1132-1135.

8. REFERENCES

*Pifer JW, Friedlander BR, Kintz RT, et al. 1989. Absence of toxic effects in silver reclamation workers. Scand J Work Environ Health 15:210-221.

Pokorny J. 1983. [A model of interaction of metal ions with the phosphate group]. Biologia (Bratisl) 38:289-292. (German).

Polachek AA, Cope CB, Williard RF, et al. 1960. Metabolism of radioactive silver in a patient with carcinoid. J Lab Clin Med 56:499-505.

Pratt JR, McCormick PV, Pontasch KW, et al. 1988. Evaluating soluble toxicants in contaminated soils. Water Air Soil Pollut 37:293-307.

Prose PH. 1963. An electron microscopic study of human generalized argyria. Am J Pathol 42:293-299

Quijada S, Soza X, Croxatto HB. 1978. Fertility inhibition by intraoviductal copper beads in rabbits. Contraception 17:553-562.

*Ragaini RC, Ralston HR, Roberts N. 1977. Environmental trace metal contamination in Kellogg, Idaho, near a lead smelting complex. Environ Sci Technol 11:773-781.

*Rains TC, Watters RL Jr, Epstein MS. 1984. Application of atomic absorption and plasma emission spectrometry for environmental analysis. Environment International 10:163-168.

Ramelow GJ, Maples RS, Thompson RL, et al. 1987. Periphyton as monitors for heavy metal pollution in the Calcasieu River estuary. Environ Poll 43:247-263.

Raskin RB. 1984. Toxicity of silver amalgam: Fact or fiction. NY State Dent J 50:582, 585, 587.

*Rattonetti A. 1974. Determination of soluble cadmium, lead, silver, and indium in rainwater and stream water with the use of flameless atomic absorption. Anal Chem 46:739.

Rauber A, Bruner B. 1987. Ingestion of concentrated silver nitrate: A report of two cases. Vet Hum Toxicol 29:321-322.

*Rawlings GD, Samfield M. 1979. Textile plant wastewater toxicity. Environmental Science and Technology 13:160-164.

*Reese RG Jr. 1986. The minerals year book. Vol. 1, Washington, DC: US Department of the Interior, Bureau of Mines, 837-856.

8. REFERENCES

Reichenbach DD. 1985. Cardiovascular system. In: Mottet NK, ed. Environmental pathology. New York, NY: Oxford University Press, 356-367.

Reuss M. 1983. Comparison of different methods for estimating the leaching of heavy metals from coal combustion wastes. Nat Sci Tech 15:193-205.

Reymond J-L, Stoebner P, Amblard P. 1980. [Cutaneous argyria: An electron microscopic study of four cases with microanalysis X study of one case]. Ann Dermatol Venereol 107:251-255. (French).

Ribadeau Dumas JL, Larmande P, Bourin M, et al. 1978. [Is there such a thing as encephalopathy related to organic compounds of silver]. Nouv Presse Med 7:1956. (French).

Ribarov SR, Benov LC. 1981. Relationship between the hemolytic action of heavy metals and lipid peroxidation. Bioch Biophys Acta 640:721-726.

Ribarov S, Benov L. 1985. Glutathione reductase and glucose-6-phosphate dehydrogenase in erythrocytes treated with heavy metals. Acta Physiol Pharmacol Bulg 11:51-54.

Ribarov S, Benov L, Benchev I. 1986. The mechanism of AgNO3 induced lipid peroxidation in erythrocytes. Biomed Biochim Acta 45:321-330.

Ridlington JW, Whanger PD. 1981. Interactions of selenium and antioxidants with mercury, cadmium and silver. Fundam Appl Toxicol 1:368-375.

Rimerman RA, Buhler DR, Whanger PD. 1977. Metabolic interactions of selenium with heavy metals. In: Lee SD, ed. Biochemical effects of environmental pollutants. Ann Arbor, MI: Ann Arbor Science Publishers, Inc., 377-396.

*Robison SH, Cantoni O, Costa M. 1982. Strand breakage and decreased molecular weight of DNA induced by specific metal compounds. Carcinogenesis (Lond) 3:657-662.

*Robkin MA, Swanson DR, Shepard TH. 1973. Trace metal concentrations in human fetal livers. Trans Am Nucl Soc 17:97.

Roe FJC, Lancaster MC. 1964. Natural, metallic and other substances, as carcinogens. Brit Med Bull 20:127-133.

Roediger WEW. 1973. The nature of silver binding in the canine thyroid "C" cell. S Afr J Med Sci 38:17-22.

8. REFERENCES

Roesijadi G, Young JS, Drum AS, et al. 1984. Behavior of trace metals in Mytilus edulis during a reciprocal transplant field experiment. Mar Ecol Prog Ser 18:155-170.

*Rosenman KD, Moss A, Kon S. 1979. Argyria: Clinical implications of exposure to silver nitrate and silver oxide. J Occup Med 21:430-435.

*Rosenman KD, Seixas N, Jacobs I. 1987. Potential nephrotoxic effects of exposure to silver. Br J Ind Med 44:267-272.

Roshchin AV, Ordzhonikidze EK. 1986. [Metal toxicokinetics and its significance for the prevention of occupational poisoning]. Gig Tr Prof Zabol, Issue 3, 1-6. (Russian).

*Rossman TG, Molina M. 1986. The genetic toxicology of metal compounds: II. Enhancement of ultraviolet light-induced mutagenesis in Escherichia coli WP2. Environ Mutagen 8:263-271.

Roy DR, Bailey JA. 1974. Effect of silver from cloud seeding on rumen microbial function. Water Air Soil Pollut 3:343-351.

*RTECS. 1988. Registry of Toxic Effects of Chemical Substances. National Library of Medicine, National Toxicology Information Program, Bethesda, MD. December 5, 1988.

*Rungby J. 1986. Experimental argyrosis: Ultrastructural localization of silver in rat eye. Exp Mol Pathol 45:22-30.

Rungby J. 1986. Exogenous silver in dorsal root ganglia, peripheral nerve, enteric ganglia, and adrenal medulla. Acta Neuropathol (Berl) 69:45-53.

Rungby J. 1986. The silver nitrate prophylaxis of crede causes silver deposition in the cornea of experimental animals. Exp Eye Res 42:93-94.

*Rungby J. 1987. Silver-induced lipid peroxidation in mice: Interactions with selenium and nickel. Toxicology 45:135-142.

*Rungby J, Danscher G. 1983a. Neuronal accumulation of silver in brains of progeny from argyric rats. Acta Neuropathol (Berl) 61:258-262.

*Rungby J, Danscher G. 1983b. Localization of exogenous silver in brain and spinal cord of silver exposed rats. Acta Neuropathol (Berl) 60:92-98.

*Rungby J, Danscher G. 1984. Hypoactivity in silver exposed mice. Acta Pharmacol Toxicol 55:398-401.

8. REFERENCES

*Rungby J, Slomianka L, Danscher G, et al. 1987. A quantitative evaluation of the neurotoxic effect of silver on the volumes of the components of the developing rat hippocampus. Toxicology 43:261-268.

Rungby J, Ellermann-Eriksen S, Danscher G. 1987. Effects of selenium on toxicity and ultrastructural localization of silver. Arch Toxicol 61:40-45.

Rungby J, Hultman P, Ellermann-Eriksen S. 1987. Silver affects viability and structure of cultured mouse peritoneal macrophages and peroxidative capacity of whole mouse liver. Arch Toxicol 59:408-412.

Ryan DE, Holzbecher J, Stuart DC. 1978. Trace elements in scalp-hair of persons with multiple sclerosis and of normal individuals. Clin Chem 24:1996-2000.

Saffiotti U, Shubik P. 1963. Studies on promoting action in skin carcinogenesis. National Cancer Institute Monograph 10:489-506.

Sakai K, Umeda T, Yamane Y. 1985. In vitro DNA methylation by methylnitrosourea in isolated copper- or silver-preloaded rat liver nuclei. Biochemical Pharmacology 34:4071-4073.

*Sano S, Fujimori R, Takashima M, et al. 1982. Absorption, excretion and tissue distribution of silver sulphadiazine. Burns 8:278-285.

Saxena J, Howard PH. 1977. Environmental transformation of alkylated and inorganic forms of certain metals. In: Perlman D, ed. Advances in applied microbiology. Vol. 21, New York, NY: Academic Press, 185-226.

Schatz H. 1982. Unusual cases. Retina 2:189-90.

Schelenz R. 1977. Dietary intake of 25 elements by man estimated by neutron activation analysis. J Radioan Chem 37:539-548.

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

Schopf E, Schulz KH, Isensee I. 1969. [Investigations on lymphocyte transformation in mercury sensitivity. Non specific transformation due to mercury compounds]. Arch Klin Exp Derm 234:420-433. (German).

Schultka R, Schmidt R, Drosner H-P. 1971. [Histochemical localization of heavy metal in the kidneys of white rats during embryonal and postnatal development]. Acta Histochem (Jena) 40:123-130. (German).

Schulze A, Bingas B. 1968. [Meningioma development induced by a foreign body]. Beitr Neurochir 15:297-301. (German).

8. REFERENCES

*Scicchitano DA, Pegg AE. 1987. Inhibition of 06-alkylguanine-DNA-alkyltransferase by metals. Mutat Res 192:207-210.

Scott WL Jr. 1967. Silver uptake in brains of chronically gamma-irradiated rats: A study by neutron activation analysis. Radiat Res 31:522-528.

*Scott KG, Hamilton JG. 1950. The metabolism of silver in the rat with radio-silver used as an indicator. University of California Publications in Pharmacology 2:241-262.

Scott KG, Hamilton JG. 1948. The metabolism of silver [Abstract]. J Clin Invest 27:555-556.

Scott R, Norman PM. 1980. Silver deposition in arteriolar basal laminae in the cerebral cortex of argyric rats. Acta Neuropathol (Berl) 52:243-246.

*Scow K, Goyer M, Nelken L, et al. 1981. Exposure and risk assessment for silver. Report to US Environmental Protection Agency, Office of Water Regulations and Standards, Washington, D.C., by Arthur D. Little, Inc., Cambridge, MA. PB85-211993.

*Segar DA, Gilio JL. 1973. The determination of trace transition elements in biological tissues using flameless atom reservoir atomic absorption. Int J Environ Anal Chem 2:291-301.

Sharma DC, Sharma M, Rathore AS, et al. 1980. Effect of silver, gold, and mercury colloids on erythrocyte and iron metabolism. Indian J Exp Biol 18:1309-1311.

Shaver SL, Mason KE. 1951. Impaired tolerance to silver in vitamin E deficient rats. Anat Rec 109:382.

Shaw EB. 1980. Questions the need for prophylaxis with silver nitrate. Pediatrics 59:792.

*Shelton D, Goulding R. 1979. Silver poisoning associated with an antismoking lozenge [letter]. Br Med J, January 27; 1(6158):267.

*Shimamoto Y, Shimamoto H. 1987. Systemic argyria secondary to breath freshener "Jintan Silver Pills". Hiroshima J Med Sci 36:245-247.

*Shouse SS, Whipple GH. 1931. I. Effects of the intravenous injection of colloidal silver upon the hematopoietic system in dogs. Jour Exp Med 53:413-420.

8. REFERENCES

Siemiatycki J Gerin M, Hubert J. 1981. Exposure-based case control approach to discovering occupational carcinogens: Preliminary findings. In: Peto R, Schneiderman M, eds. Quantification of occupational cancer, Banbury Report No. 9. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 471-481.

Silver Institute. 1975. Silver guards good health. Silver Inst. Lett. 5(5):1.

Sirover MA, Loeb LA. 1976. Infidelity of DNA synthesis in vitro: Screening for potential metal mutagens or carcinogens. Science 194:1434-1436.

Sittig M. 1985. Silver and Compounds. Handbook of toxic and hazardous chemicals and carcinogens. 2nd ed. Park Ridge, NJ: Noyes Data Corporation, 789-790.

Skouby SO, Tabor A. 1978. [Experience with a copper-silver IUD, Cu-T 2200 W]. Ugeskr Laeg 140:1882-1885. (Danish).

Smirnov VG. 1983. [Experimental studies of toxicology of silver and establishment of maximum permissible levels for its compounds in the air of worksites]. Gig Tr Prof Zabol, Issue 12, 33-37. (Russian).

Smith DR, Stephenson MD, Flegal AR. 1986. Trace metals in mussels transplanted to San Francisco Bay. Environmental Toxicology and Chemistry 5:129-138.

*Smith IC, Carson BL. 1977. Trace metals in the environment, Vol. 2. Silver. Ann Arbor, MI: Ann Arbor Science Publishers, Inc.

Smith TJ, Blough S. 1982. Chromium, manganese, nickel,and other elements. In: Rom WN, ed. Environmental and occupational medicine. Boston, MA: Little, Brown and Co., 491-510.

*Snider EH, Manning FS. 1982. A survey of pollutant emission levels in waste waters and residuals from the petroleum refining industry. Environment International 7:237-258.

*Snyder WS, et al. 1975. Report of the task group on reference man. Oxford, England: Pergamon Press, 407-708.

*Soldatenkova NA, Smirnov VG. 1983. [Atomic absorption method of determining silver in the air]. Gig Tr Prof Zabol, Issue 6, 53-54. (Russian).

Spiegel L. 1931. A discoloration of the skin and mucous membranes resembling argyria, following the use of bismuth and silver arsphenamine. Archives of Dermatology and Syphilology 23:266-286.

8. REFERENCES

Spielman A, Gutman D, Laufer D. 1981. Anesthesia following endodontic overfilling with AH26. Report of a case. Oral Surg Oral Med Oral Pathol 52:554-556.

Splittgerber AG, Tappel AL. 1979. Inhibition of glutathione peroxidase by cadmium and other metal ions. Arch Biochem Biophys 197:534-542.

Stammberger H. 1982. [Argyrosis of the nasal mucosa]. Laryng Rhinol Otol (Stuttg) 61:234-237. (German).

Stanley JS. 1986. Broad scan analysis of the FY82 national human adipose tissue survey specimens. Volume 1. Executive Summary. Washington, DC: US Environmental Protection Agency, Office of Toxic Substances, Design and Development Branch, National Human Monitoring Program. EPA 560/5-86-035.

*Starkey BJ, Taylor AP, Walker AW. 1987. Measurement of silver in blood by electrothermal atomic absorption spectrometry (ET-AAS). Ann Clin Biochem 24:SI91-SI93.

Starzynska T, Mandat A. 1987. [A case of argyria after peroral treatment of peptic ulcer with silver albuminate]. Wiad Lek 40:691-693. (Polish).

Stephenson T, Lester JN. 1987. Heavy metal behavior during the activated sludge process I. Extent of soluble and insoluble metal removal. Sci Total Environ 63:199-214.

Stephenson T, Lester JN. 1987. Heavy metal behavior during the activated sludge process II. Insoluble metal removal mechanisms. Sci Total Environ 63:215-230.

*Stokinger HE. 1981. The metals. In: Clayton GD, Clayton FE, eds. Patty's industrial hygiene and toxicology. Vol. 2A, 3rd ed. New York, NY: John Wiley and Sons, Inc., 1881-1894.

Strassburg M, Schubel F. 1967. [Generalized allergic reaction caused by silver amalgam fillings]. Deutsch Zahnarztuche Zeitschrift 22:3-9. (German).

Strauch B, Buch W, Grey W, et al. 1969. Methemoglobinemia: A complication of silver nitrate therapy used in burns. AORN Journal 10:54-56.

Strauch B, Buch W, Grey W, et al. 1969. Successful treatment of methemoglobinemia secondary to silver nitrate therapy. New England Journal of Medicine 281:257-258.

Strong CR, Luoma SN. 1981. Variations in the correlation of body size with concentrations of copper and silver in the bivalve Macoma balthica. Can J Fish Aquat Sci 38:1059-1064.

8. REFERENCES

*Struempler AW. 1975. Trace element composition in atmospheric particulates during 1973 and the summer of 1974 at Chadron, Neb. Environ Sci Technol 9:1164-1168.

Sugawara N, Sugawara C. 1984. Effect of silver on ceruloplasmin synthesis in relation to low-molecular-weight protein. Toxicology Letters 20:99-104.

Suissa M. 1983. Spectrophotometric quantitation of silver grains eluted from autoradiograms. Anal Biochem 133:511-514.

Sujari ANA, Bowen HJM. 1986. Interactions of silver with humates and other species in natural waters. J Radioanal Nucl Chem 106:213-222.

Sunderman FW Jr. 1987. Metal induction of heme oxygenase. In: Silbergeld EK, Fowler RA, eds. Annals of the New York Academy of Sciences. Vol. 514, New York, NY: New York Academy of Sciences, 65-80.

Swanson AB, Wagner PA, Ganther HE, et al. 1974. Antagonistic effects of silver and tri-o-cresyl phosphate on selenium and glutathione peroxidase in rat liver and erythrocytes [Abstract]. Fed Proc 33:693.

Tan E-L, Williams MW, Schenley RL, et al. 1984. The toxicity of sixteen metallic compounds in Chinese hamster ovary cells. Toxicol Appl Pharmacol 74:330-336.

*Tanita Y, Kato T, Hanada K, et al. 1985. Blue macules of localized argyria caused by implanted acupuncture needles. Electron microscopy and roentgenographic microanalysis of deposited metal. Arch Dermatol 121:1550-1552.

Temple RM, Farooqi AA. 1985. An elderly, slate-grey woman. Practitioner 229:1053-1054.

Teraok H. 1981. Distribution of 24 elements in the internal organs of normal males and the metallic workers in Japan. Archives of Environmental Health 36:155-165.

*Terhaar CJ, Ewell WS, Dziuba SP, et al. 1977. A laboratory model for evaluating the behavior of heavy metals in an aquatic environment. Water Research 11:101-110.

Terner K, Javor R. 1982. The effect of PGF2a on human oral mucous membrane. Pharmacol Res Commun 14:511-522.

*The International Technical Information Institute (ITII). 1982. Toxic and hazardous industrial chemicals safety manual. Tokyo, Japan: International Technical Information Institute, 464-465.

8. REFERENCES

Theodossiadis G, Kouris T, Papadopoulou C. 1982. Determination of trace element Ag and Sc concentrations in human cataractous lenses. Ophthalmic Res 14:436-441.

*The Silver Institute. 1988. Silver consumption in the photographic industry. The Silver Institute, Washington, DC. 20008.

*The Silver Institute. 1990. Latest Silver Institute refining statistics. The Silver Institute, Inc., Washington, DC. 20008.

Thompson JD, Nechay BR. 1981. Inhibition by metals of a canine renal calcium, magnesium activated adenosine triphosphatase. J Toxicol Environ Health 7:901-908.

*Thomson EA, Luoma SN, Johansson CE, et al. 1984. Comparison of sediments and organisms in identifying sources of biologically available trace metal contamination. Water Research 18:755-766.

Thorlacius-Ussing O, Rungby J. 1984. Ultrastructural localization of exogenous silver in the anterior pituitary gland of the rat. Exp Mol Pathol 41:58-66.

Thorlacius-Ussing O, Graabaek PM. 1986. Simultaneous ultrastructural demonstration of heavy metals (silver, mercury) and acid phosphatase. Histochemical Journal 18:639-646.

Tichy P, Rosina J, Blaha K Jr, et al. 1986. Biliary excretion of 110mAg and its kinetics in the isolated perfused liver. J Hyg Epidemiol Microbiol Immunol 30:145-148.

Timperley MH. 1978. Collaborative tests of water analysis (the CHEMAQUA program). New Zealand Journal of Science 21:557-564.

Tipton IH, Cook MJ. 1963. Trace elements in human tissue. Part II. Adult subjects from the United States. Health Phys 9:103-145.

*Tipton IH, Stewart PL, Martin PG. 1966. Trace elements in diets and excreta. Health Phys 12:1683-1689.

Tomokuni K. 1979. Interaction of zinc and other metals on the activity of erythrocyte delta- aminolevulinic acid dehydratase in vitro. J Toxicol Sci 4:11-18.

Tomokuni K, Ogata M. 1980. Comparative study of effects of lead on the activity of erythrocyte pyrimidine 5'-nucleotidase and delta-aminolevulinate dehydratase in vivo and in vitro. Arch Toxicol 45:197-201.

8. REFERENCES

Tomokuni K, Ogata M. 1980. [In-vitro effect of heavy metals on the activity of pyrimidine 5' nucleotidase and gamma amino levulinate dehydratase in the human erythrocyte]. Jap J Ind Health 22:282-283. (Japanese).

Tomza U, Janicki T, Kossman S. 1983. Instrumental neutron activation analysis of trace elements in hair: A study of occupational exposure to a non-ferrous smelter. Radiochem and Radioanal Letters 58:209-220.

*Ulitzur S, Barak M. 1988. Detection of genotoxicity of metallic compounds by bacterial bioluminescence test. Journal of Bioluminescence and Chemiluminescence 2:95-99.

Underwood EJ. 1979. Interactions of trace elements. In: Oehme FW, ed. Hazardous and toxic substances. Vol. 2, New York, NY: Marcel Dekker, Inc., 641-668.

Valente P, Axelrod JL. 1978. Acute leukopenia associated with silver sulfadiazine therapy. J Trauma 18:146-147.

Van Campen DR. 1966. Effects of zinc, cadmium, silver and mercury on the absorption and distribution of copper-64 in rats. J Nutr 88:125-130.

Van Vleet JF. 1976. Induction of lesions of selenium-vitamin E deficiency in pigs fed silver. Am J Vet Res 37:1415-1420.

*Van Vleet JF. 1977. Protection by various nutritional supplements against lesions of selenium- vitamin E deficiency induced in ducklings fed tellurium or silver. Am J Vet Res 38:1393-1398.

Van Vleet JF. 1982. Amounts of twelve elements required to induce selenium-vitamin E deficiency. Am J Vet Res 43:851-857.

*Van Vleet JF, Boon GD, Ferrans VJ. 1981. Induction of lesions of selenium-vitamin E deficiency in ducklings fed silver, copper, cobalt, tellurium, cadmium, or zinc: Protection by selenium. Am J Vet Res 42:1206-1217.

Venugopal B, Luckey TD. 1978. Introduction to heavy metal toxicity in mammals. Metal toxicity in mammals. Vol. 2, New York, NY: Plenum Press, 36-37.

Veron C, Hildebrand HF, Martin P. 1986. [Dental amalgams and allergy]. J Biol Buccale 14:83-100. (French).

*VIEW Database. 1989. Agency for Toxic Substances and Disease Registry (ATSDR), Office of External Affairs, Exposure and Disease Registry Branch, Atlanta, GA. February 21, 1989.

8. REFERENCES

Vik H, Andersen KJ, Julshawn K, et al. 1985. Neuropathy caused by silver absorption from arthroplasty cement [letter]. Lancet, April 13; 1(8433):872.

*Vince DG, Williams DF. 1987. Determination of silver in blood and urine by graphite furnace atomic absorption spectrometry. The Analyst 112:1627-1629.

Von Mallinckrodt MG, Pooth M. 1969. [Simultaneous spectrographic testing for 25 metals and metaloids in biological material]. Arch Toxikol 25:5-18. (German).

Von Rosen G. 1954. Breaking of chromosomes by the action of elements of the periodical system and by some other principles. Hereditas 40:258-263.

Von Rosen G. 1957. Mutations induced by the action of metal ions in pisum. Hereditas 43:644-664.

Wagner PA, Hoekstra WG, Ganther HE. 1975. Alleviation of silver toxicity by selenite in the rat in relation to tissue glutathione peroxidase. Proc Soc Exp Biol Med 148:1106-1110.

*Wahlberg JE. 1965. Percutaneous toxicity of metal compounds. A comparative investigation in guinea pigs. Arch Environ Health 11:201-204.

Walberg JE. 1982. Metals and skin. In: Malbach HI, Gellin GA, eds. Occupational and industrial dermatology. Chicago, IL: Year Book Medical Publishers, Inc., 346-350.

*Walker F. 1971. Experimental argyria: A model for basement membrane studies. Br J Exp Pathol 52:589-593.

Wallace A, Alexander GV, Chaudhry FM. 1977. Phytotoxicity of cobalt, vanadium, titanium, silver, and chromium. Communication in Soil Science and Plant Analysis 8:751-756.

*Ward NI, Roberts E, Brooks RR. 1979. Silver uptake by seedlings of Lolium perenne L. and Trifolium repens L. New Zealand Journal of Science 22:129-132.

*WDHSS. 1989. Written communication regarding State of Wisconsin regulation of silver levels in groundwater. Madison, WI: Wisconsin Department of Health and Social Services. (June 8).

*Weast RC, Astle MJ, Beyer WH, ed. 1988-1989. Handbook of chemistry and physics. 69th ed. Boca Raton, FL: CRC Press, Inc.

*Webster DA, Spadaro JA, Becker RO, et al. 1981. Silver anode treatment of chronic osteomyelitis. Clinical Orthopedics and Related Research 161:105-114.

8. REFERENCES

Weir FW. 1979. Health hazard from occupational exposure to metallic copper and silver dust. American Industrial Hygiene Association Journal 40:245-247.

*Weiss G, ed. 1986. Hazardous chemicals data book. 2nd ed. Park Ridge, NJ: Noyes Data Corporation, 887-893.

Weitzenblum S, Peter J-D, Zawislak PR, et al. 1977. [Argyria: Apropos of a case in a child]. Pediatrie 32:371-375. (French).

Wenzloff DR. 1976. Distribution and abundance of heavy metals in finfish, invertebrates, and sediments collected at a deepwater disposal site. Marine Pollution Bulletin 7:185-187.

West HD, Goldie H. 1956. Topical localization in mouse of radioactive silver oxide (Ag111)20 introduced by various routes. Proc Soc Exp Biol Med 92:116-120.

West HD, Elliott RR, Johnson AP, et al. 1950. In vivo localization of radioactive silver at predetermined sites in tissues. American Journal Roentgenology Radium Therapy 64:831-834.

Weston RF, Chairman PE, Morrell RA. 1977. Treatment of water and waste water for removal of heavy metals. Viruses and trace contaminants in water and wastewater. Ann Arbor, MI: Ann Arbor Science Publishers, Inc., 167-181.

Whanger PD. 1976. Selenium versus metal toxicity in mammals. Proceedings of the Symposium on Selenium-Tellurium in the Environment:234-252.

Whanger PD. 1985. Metabolic interactions of selenium with cadmium, mercury, and silver. Adv Nutr Res 7:221-250.

Whanger PD, Weswig PH, Schmitz JA, et al. 1976. Effects of selenium, cadmium, mercury, tellurium, arsenic, silver and cobalt on white muscle disease in lambs and effect of dietary forms of arsenic. Nutrition Reports International 14:63-72.

White IR, Rycroft RJG. 1982. Contact dermatitis from silver fulminate-fulminate itch. Contact Dermatitis 8:159-163.

*Whitlow SI, Rice DL. 1985. Silver complexation in river waters of central New York. Water Res. 19:619-626.

Wilhelm FX, Daune M. 1969. [Interactions of metallic ions with DNA. III. Stability and configuration of Ag-DNA complexes]. Biopolymers 8:121-137. (French).

8. REFERENCES

*Windholz M, ed. 1983. The Merck index. 10 ed. Rahway, NJ: Merck & Co., Inc., 8338, 8343, 8352-8357.

Wise SA, Zeisler R. 1984. The pilot environmental specimen bank program. Environ Sci Technol 18:302a-307a.

Wood M. 1965. Silver nitrate and burns--caution. Ariz Med 2:817.

Wright DC, Gallant RF, Spangberg L. 1982. Correlation of corrosion behavior and cytotoxicity in Au-Cu-Ag ternary alloys. J Biomed Mater Res 16:509-517.

Wysor MS. 1975. Orally administered silver sulfadiazine: Chemotherapy and toxicology in CF-1 mice; Plasmodium berghei (malaria) and Pseudomonas aerygubis. Chemotherapy 21:302-310.

Yatomi H. 1986. Study on the interaction of trace metals, silver and copper. J Yonago Med Ass 37:405-414.

Yatomi H, Nose T, Sugiyama K, et al. 1983. [The interaction between silver and copper in the rat]. Igaku to Seibutsugaku 107:265-267. (Japanese).

Yoshida M, Tashiro H, Iwami K, et al. 1983. Bioavailability of selenite, selenomethionine and selenocystine in rats with silver loading. Agric Biol Chem 47:807-813.

Yoshikawa H. 1970. Preventive effect of pretreatment with low dose of metals on the acute toxicity of metals in mice. Ind Health 8:184-191.

Zakour RA, Kunkel TA, Loeb LA. 1981. Metal-induced infidelity of DNA synthesis. Environ Health Perspect 40:197-205.

Zech P, Colon S, Labeeuw R, et al. 1973. [Nephrotic syndrome with deposits in the glomerular basement membranes during argyria]. Nouv Presse Med 2:161-164. (French).

Zegarelli EV, Kutscher AH. 1978. Toxicity reactions. In: Zegarelli EV, Kutscher AH, Hyman GA, eds. Diagnosis of diseases of the mouth and jaws. 2nd ed. Philadelphia, PA: Lea & Febiger, 327-331.

Zieker AW, Wisnicki J. 1979. Corneal burns from watch battery explosion. Am J Ophthalmol 88:798-9.

9. GLOSSARY

Acute Exposure -- Exposure to a chemical for a duration of 14 days or less, as specified in the toxicological profiles.

Adsorption Coefficient (Koc) -- The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd) -- The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Bioconcentration Factor (BCF) -- The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Cancer Effect Level (CEL) -- The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen -- A chemical capable of inducing cancer.

Ceiling Value -- A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure -- Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Developmental Toxicity -- The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Embryotoxicity and Fetotoxicity -- Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

9. GLOSSARY

EPA Health Advisory -- An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH) -- The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

Intermediate Exposure -- Exposure to a chemical for a duration of 15-364 days as specified in the Toxicological Profiles.

Immunologic Toxicity -- The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In Vitro -- Isolated from the living organism and artificially maintained, as in a test tube.

In Vivo -- Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO}) -- The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50}) -- A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{LO}) -- The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50}) -- The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50}) -- A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL) -- The lowest dose of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Malformations -- Permanent structural changes that may adversely affect survival, development, or function.

9. GLOSSARY

Minimal Risk Level -- An estimate of daily human exposure to a chemical that is likely to be without an appreciable risk of deleterious effects (noncancerous) over a specified duration of exposure.

Mutagen -- A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity -- The occurrence of adverse effects on the nervous system following exposure to chemical.

No-Observed-Adverse-Effect Level (NOAEL) -- The dose of chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (Kow) -- The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Permissible Exposure Limit (PEL) -- An allowable exposure level in workplace air averaged over an 8-hour shift.

q_1* -- The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually μg/L for water, mg/kg/day for food, and $\mu g/m^3$ for air).

Reference Dose (RfD) -- An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ) -- The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 lb or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

9. GLOSSARY

Reproductive Toxicity -- The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Short-Term Exposure Limit (STEL) -- The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

Target Organ Toxicity -- This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen -- A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV) -- A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-Weighted Average (TWA) -- An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose (TD_{50}) -- A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Uncertainty Factor (UF) -- A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX

PEER REVIEW

A peer review panel was assembled for silver. The panel consisted of the following members: Dr. Rajendar Abraham, Abraham Associates Limited, Albany, NY; Dr. Thomas Hinesly, University of Illinois, IL; Dr. Arthur Furst, University of San Francisco, CA; Dr. Ernest Foulkes, University of Cincinnati, OH. These experts collectively have knowledge of silver's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(i)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

A joint panel of scientists from ATSDR and EPA has reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the Agency for Toxic Substances and Disease Registry.