DRAFT
TOXICOLOGICAL PROFILE FOR
TUNGSTEN

Prepared for:

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

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DISCLAIMER

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UPDATE STATEMENT

Toxicological profiles are revised and republished as necessary. For information regarding the update status of previously released profiles, contact ATSDR at:

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

FOREWORD

This toxicological profile is prepared in accordance with guidelines* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is 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.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning 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 are identified by ATSDR and EPA.

Each profile includes the following:

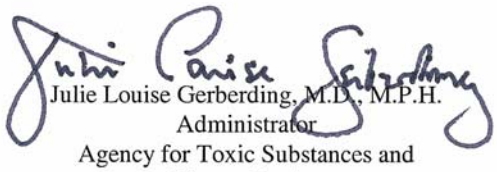
(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(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 that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

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.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.



Julie Louise Gerberding, M.D., M.P.H.
Administrator
Agency for Toxic Substances and
Disease Registry

*Legislative Background

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on October 25, 2001 (66 FR 54014). For prior versions of the list of substances, see *Federal Register* notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17,1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); February 28, 1994 (59 FR 9486); April 29, 1996 (61 FR 18744); November 17, 1997 (62 FR 61332); and October 21, 1999 (64 FR 56792). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by type of health effect (death, systemic, immunologic, reproductive), by route of exposure, and by length of exposure (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.

NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Section 1.6 How Can (Chemical X) Affect Children?
Section 1.7 How Can Families Reduce the Risk of Exposure to (Chemical X)?
Section 3.7 Children's Susceptibility
Section 6.6 Exposures of Children

Other Sections of Interest:

Section 3.8 Biomarkers of Exposure and Effect
Section 3.11 Methods for Reducing Toxic Effects

ATSDR Information Center

Phone: 1-888-42-ATSDR or (404) 498-0110 ***Fax:*** (404) 498-0093
E-mail: atsdric@cdc.gov ***Internet***: http://www.atsdr.cdc.gov

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental Hazards; Skin Lesions and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity*; and numerous chemical-specific case studies.

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-NIOSH.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212.

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 55 West Seegers Road, Arlington Heights, IL 60005 • Phone: 847-818-1800 • FAX: 847-818-9266.

CONTRIBUTORS

CHEMICAL MANAGER(S)/AUTHOR(S):

Sam Keith, M.S., C.H.P
Daphne B. Moffett, Ph.D.
Zemoria A. Rosemond, B.A.
ATSDR, Division of Toxicology, Atlanta, GA

David W. Wohlers, Ph.D.
Richard J. Amata, M.S.
Gary L. Diamond, Ph.D.
Syracuse Research Corporation, Syracuse, NY

THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific minimal risk levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

3. Data Needs Review. The Research Implementation Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

PEER REVIEW

A peer review panel was assembled for tungsten. The panel consisted of the following members:

1. Finis Cavender, Ph.D., DABT, CEI, Consultant in Toxicology, 310 Lightwood Knot Road, Greer, South Carolina 29651;

2. Robert Michaels, Ph.D., President, RAM TRAC Corporation, Toxicology & Risk Assessment Consulting, 3100 Rosendale Road, Schenectady, New York 12309; and

3. Raghubir Sharma, Ph.D., Fred C. Davison Distinguished Chair in Toxicology, Department of Physiology and Pharmacology, The University of Georgia, Athens, Georgia 30602.

These experts collectively have knowledge of tungsten'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.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have 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 ATSDR.

CONTENTS

LIST OF FIGURES

LIST OF TABLES

1. PUBLIC HEALTH STATEMENT

This public health statement summarizes general information about tungsten and the effects of exposure.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal cleanup activities. Tungsten has been found in at least 6 of the 1,636 current or former NPL sites. However, the total number of NPL sites evaluated for this substance is not known. As more sites are evaluated, the sites at which tungsten is found may increase. This information is important because these sites may be sources of exposure.

When a substance 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. This release does not always lead to exposure. You are exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance, or by skin contact.

If you are exposed to tungsten, many factors determine whether you'll be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it. You must also consider the other chemicals you're exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT IS TUNGSTEN?

Tungsten is a naturally occurring element that, in most environments, is a solid. In nature, it occurs in rocks and soil as minerals, but never as the pure metal. Two kinds of tungsten-bearing mineral rocks, called wolframite and scheelite, are mined commercially. The mineral ore is processed to recover the tungsten and turn it into either chemical compounds or metal. Elemental tungsten, like elemental copper or gold, is a metal. Its color can range from tin white (for the pure metal) to steel gray (for metal that has impurities in it). Tungsten can be used as a pure metal or mixed with other metals to make alloys. Tungsten alloys tend to be strong and

flexible, resist wear, and conduct electricity well. Tungsten and its alloys are used as light bulb filaments, as the part of x-ray tubes where x-rays are formed, as a catalyst to speed up chemical reactions, as a component of steel in high-speed tools, in phonographic needles, as welding electrodes, and as gyroscope wheels. They can be used in bullets (as a replacement for lead) and in armor penetrators (as a substitute for depleted uranium). Chemical compounds of tungsten are used for many purposes. Cemented tungsten carbide, a hard substance used to make grinding wheels and cutting or forming tools, is the most common tungsten compound. Other tungsten compounds are used in ceramic pigments, as fire retardant coatings for fabrics, and as color-resistant dyes for fabrics. More information on the chemical, physical properties, production, and uses of tungsten and its compounds are presented in Chapters 4, 5, and 6.

1.2 WHAT HAPPENS TO TUNGSTEN WHEN IT ENTERS THE ENVIRONMENT?

Tungsten occurs naturally in the environment, in minerals, but not as the pure metal. As an element, tungsten can be neither created nor destroyed chemically, although tungsten can change forms in the environment.

Tungsten is released into air as fine dust-like particles by weathering. Emissions from hard metal industries also increase tungsten levels in air. The amount of tungsten that has been measured in the ambient air is, in general, less than 10 billionths of a gram per cubic meter (or parts per billion [ppb]). Very small dust particles of tungsten in the air fall out onto surface water, plant surfaces, and soil either by themselves or when rain or snow falls. These tungsten particles eventually recycle back in the soil or in the bottoms of lakes, rivers, and ponds, where they stay and mix with tungsten that is already there.

Tungsten in water originates mainly from dissolution of tungsten from rocks and soil that water runs over and through. Tungsten has not been detected in the vast majority of surface water and groundwaters of the United States. Some exceptions include areas near mines and natural deposits, and also in Fallon, Nevada, where tungsten has been detected in municipal water and groundwater. Only a very small fraction of tungsten in water originates from the settling of dust out of the air. Most tungsten products of human-origin that enter waterways originate from industry discharges of waste water. Tungsten in water may be in either soluble or insoluble

forms. Insoluble tungsten in water can settle to the bottom where it enters sediment. Some insoluble tungsten compounds, however, can remain suspended in ocean water for many years, requiring as long as 1,000 years to settle to the bottom.

Tungsten occurs naturally in soil as a mineral, or component of soil. It occurs in amounts that vary over a wide range from less than 1 to as high as 83 thousandths of a gram per kilogram of soil. Another way to say this is that the soil concentration ranges from 1 to 83 parts per million (ppm). Disposal of coal ash, incinerator ash, and industrial wastes may increase the amount of tungsten in soil. A portion of tungsten in soil does not dissolve in water, but remains bound and is not likely to move deeper into the ground and enter groundwater. The remaining soluble portion may move deeper into the ground and enter groundwater if the pH is greater than 7. In the environment, chemical reactions can change the water-soluble tungsten compounds into insoluble forms. In some cases, water-insoluble tungsten compounds can change to soluble forms. In general, exposure to water-soluble tungsten compounds in the environment will pose a greater threat to human health than water-insoluble forms. More information about the fate and movement of tungsten in the environment is presented in Chapter 6.

1.3 HOW MIGHT I BE EXPOSED TO TUNGSTEN?

You can be exposed to low levels of tungsten by breathing air or eating food that contains tungsten. The average ambient concentration of tungsten in air has been reported to be less than 0.5 nanograms in a cubic meter of air (1 nanogram is 1 billionth of a gram). Cities have higher levels of tungsten in the air because tungsten is released from industry. Tungsten has been detected in municipal water from Fallon, Nevada. However, the amounts of tungsten in drinking water are generally not known. This is probably because the tungsten levels are lower than the laboratory methods are able to detect without concentrating samples, or the laboratory does not measure for tungsten. The amounts in foods are generally not known, possibly for the same reasons. For residents of the European Community, beverages significantly contributed to the total dietary intake of tungsten. The average concentration of tungsten in beverages ranged from 0.31 to 7.4 micrograms per liter of water (1 microgram is 1 millionth of a gram). Tungsten in plants was either taken up by the plant or was attached to the plant as a component of the soil. The concentration of tungsten in onions collected from Denmark is 17 micrograms in a kilogram

of fresh vegetables. Although very limited data are available, exposure to tungsten from air, drinking water, and food is expected to be insignificant.

In certain workplaces, you can be exposed to levels of tungsten in air that are higher than background levels, which are very small or none. Exposures are mostly in the form of tungsten metal or tungsten carbide. Occupational exposure to tungsten occurs primarily at places where individuals use hard metals containing tungsten or are engaged in the machining of these metals. This includes the grinding (pointing) of tungsten metal welding electrodes prior to use. Occupational exposure to tungsten carbide occurs during the machining of tungsten carbide tools in the manufacturing process. The total number of individuals occupationally exposed to tungsten or its compounds has been estimated to be about 68,000.

Tungsten metal and metal alloys occur in consumer products such as electronics, light bulbs filaments, cemented tungsten carbide grinding wheels, carbide tipped tools, and “green” bullets. No other consumer products or products used in crafts, hobbies, or cottage industries were identified that contain significant amounts of tungsten. It is unlikely that tungsten present in consumer products poses a hazard. However, appropriate dust masks are recommended for amateur craftsmen engaging in activities that may potentially produce tungsten carbide dust (e.g., metal grinding). More information about tungsten exposure is discussed in Chapter 6.

1.4 HOW CAN TUNGSTEN ENTER AND LEAVE MY BODY?

Tungsten can enter your body from the food you eat or the water you drink, from the air you breathe, or from contact with the skin. When you eat, drink, breathe, or touch things containing tungsten compounds that can easily be dissolved in water, tungsten enters your blood and is carried to all parts of your body. Most of the tungsten that enters your blood is rapidly released from your body in the urine. When you eat or drink things containing tungsten, much of the tungsten passes through your digestive system and is released from your body in the feces. When you breathe air that contains tungsten, some of the tungsten moves quickly to your bloodstream from the lungs, and some of the tungsten is cleared from your lungs in mucus that is either swallowed or spit out. When you swallow tungsten that was first in your lungs, it passes through your digestive system as if you had eaten it. Some enters your blood from your

digestive system and some passes out with the feces. A small portion of the tungsten that enters your blood may spend some time in bone, fingernails, or hair. Some of this tungsten is slowly eliminated from your body through the urine and feces.

1.5 HOW CAN TUNGSTEN AFFECT MY HEALTH?

To protect the public from the harmful effects of toxic chemicals and to find ways to treat people who have been harmed, scientists use many tests.

One way to see if a chemical will hurt people is to learn how the chemical is absorbed, used, and released by the body; for some chemicals, animal testing may be necessary. Animal testing may also be used to identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method to get information needed to make wise decisions to protect public health. Scientists have the responsibility to treat research animals with care and compassion. Laws today protect the welfare of research animals, and scientists must comply with strict animal care guidelines.

You are not likely to experience any health effects that would be related to exposure to tungsten or tungsten compounds. Tungsten compounds have caused breathing problems and changed behavior in some animals given very large amounts of tungsten compounds, but you are not likely to be exposed to amounts of tungsten in the air you breathe or the food or water you take into your body that would be large enough to cause similar effects.

1.6 HOW CAN TUNGSTEN AFFECT CHILDREN?

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans.

Children could be affected in the same ways as adults. In adult animals, very large amounts of tungsten compounds have been shown to cause breathing problems and changes in behavior. However, it is not likely that children would be exposed to amounts of tungsten in the air they

breathe or the food or water they consume that would be large enough to cause effects similar to those that were seen in the animals. Animal studies have shown that tungsten in the blood of a pregnant mother can enter the blood of a fetus in the womb. Studies in dairy cows have shown that tungsten may also enter the milk. There is no information to suggest that the effects seen in animals could not occur in humans. We do not know whether unborn babies, babies, and children might differ from adults in their susceptibility to health effects from exposure to tungsten or tungsten compounds.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO TUNGSTEN?

If your doctor finds that you have been exposed to significant amounts of tungsten, ask whether your children might also have been exposed. Your doctor might need to ask your state health department to investigate.

Children living near waste sites containing tungsten are likely to be exposed to higher environmental levels of tungsten through breathing, drinking contaminated drinking water, touching soil, and eating contaminated soil. Children sometimes eat dirt, which should be discouraged. Parents should supervise to see that children wash their hands frequently and before eating. Parents should consult their family physicians about whether (and how) hand-to-mouth behaviors in their children might be discouraged. If your community's drinking water has been reported to contain elevated levels of tungsten, you should take advantage of alternative water sources such as bottled water for drinking. Some children may be exposed to tungsten by contact with a family member who works in a facility using tungsten or who works with tungsten carbide grinding wheels. If you work at a facility that uses tungsten or have tungsten dust on your clothes, change your clothes and clean your hair and skin before leaving your job or work site and returning home. Do not bring objects home such as work tools that may be contaminated with tungsten.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO TUNGSTEN?

Medical tests exist that can determine whether your body fluids contain high levels of tungsten. Samples of blood or feces can be collected in a doctor's office and sent to a laboratory that can measure tungsten levels. It is easier for most laboratories to measure tungsten in blood than in feces. The presence of high levels of tungsten in the feces can mean recent high tungsten exposure. High levels of tungsten in the blood can mean high tungsten consumption and/or high exposure. High tungsten levels in blood or feces reflect the level of exposure to tungsten. Measuring tungsten levels in urine and saliva also may provide information about tungsten exposure. Tests to measure tungsten in hair may provide information on long-term tungsten exposure. More information on tests to measure tungsten in the body is located in Chapter 7.

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

The federal government develops regulations and recommendations to protect public health. Regulations can be enforced by law. Federal agencies that develop regulations for toxic substances include the Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA). Recommendations provide valuable guidelines to protect public health but cannot be enforced by law. Federal organizations that develop recommendations for toxic substances include the Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH).

Regulations and recommendations can be expressed in not-to-exceed levels in air, water, soil, or food that are usually based on levels that affect animals; then they are adjusted to help protect people. Sometimes these not-to-exceed levels differ among federal organizations because of different exposure times (an 8-hour workday or a 24-hour day), the use of different animal studies, or other factors.

Recommendations and regulations are also periodically updated as more information becomes available. For the most current information, check with the federal agency or organization that provides it. Some regulations and recommendations for tungsten include the following:

There are few guidelines for tungsten and tungsten compounds. For tungsten and insoluble tungsten compounds, NIOSH has established a recommended exposure limit (REL; 10-hour time weighted average) of 5 mg/m^3 and a short-term exposure limit (STEL; 15-minute time weighted average) of 10 mg/m^3. OSHA has established permissible exposure limits (PELs; 8-hour time weighted average) for tungsten of 5 mg/m^3 (insoluble compounds) and 1 mg/m^3 (soluble compounds) for construction and shipyard industries.

More information on regulations and guidelines is available in Chapter 8.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below.

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses resulting from exposure to hazardous substances.

Toxicological profiles are also available on-line at www.atsdr.cdc.gov and on CD-ROM. You may request a copy of the ATSDR ToxProfiles CD-ROM by calling the information and technical assistance toll-free number at 1-888-42ATSDR (1-888-422-8737), by email at atsdric@cdc.gov, or by writing at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE
Mailstop E-29
Atlanta, GA 30333
Fax: 1-404-498-0093

For-profit organizations may request a copy of final profiles from the following:

National Technical Information Service (NTIS)
5285 Port Royal Road
Springfield, VA 22161
Phone: 1-800-553-6847 or 1-703-605-6000
Web site: http://www.ntis.gov/

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO TUNGSTEN AND TUNGSTEN COMPOUNDS IN THE UNITED STATES

Tungsten is naturally released to the atmosphere by windblown dusts. Processes of human origin, such as ore processing, hard-metal fabrication, tungsten carbide production and use, and municipal waste combustion release tungsten to the atmosphere. Tungsten naturally enters waterways through the weathering of rocks and soils. Tungsten can be released to surface waters from sources of human origin (e.g., water effluents from tungsten mining). Deposition of tungsten aerosols or dusts from both natural and anthropogenic sources is also source of tungsten in surface waters. Some tungsten compounds are naturally present in soil, but the concentration of tungsten in localized soils can be increased by land application of sewage sludge, fertilizers, municipal solid waste ash, and industrial wastes that contain tungsten, or by deposition of particulate aerosols.

The general population typically has blood levels of 1–6 μg/L and urine levels of 0.085 μgL of tungsten through inhalation of air and consumption of food. The concentration of tungsten in ambient air is <10 ng/m^3. Limited monitoring data for food or drinking water were located in the United States. Levels of tungsten in these media are expected to be low. For example, onions collected from 11 Danish sites contained tungsten at a mean level of 16.7 μg/kg fresh weight. Recently, tungsten was found in the municipal water supply of Fallon, Nevada at a concentration of 25 μg/L and in household water from this community at a concentrations ranging from 0 to 217.3 μg/L. The general population typically has low levels of tungsten in their blood and urine. As part of the National Health and Nutrition Examination Survey (NHANES) conducted between the years 1999 and 2000, the mean concentration of tungsten in urine of 0.085 μg/L (n=2,338; age ≥6 years old) was reported for the U.S. population. Individuals who work in manufacturing, fabricating, and reclaiming industries, especially individuals using hard metal materials or tungsten carbide machining tools, may be exposed to higher levels of tungsten or tungsten compounds than the general population. Occupational exposure is primarily via inhalation of dust particles of elemental (metallic) tungsten and/or its compounds.

2.2 SUMMARY OF HEALTH EFFECTS

Pulmonary fibrosis, memory and sensory deficits, and increased mortality due to lung cancer have been associated with occupational exposure to dusts generated in the hard metal industry. Hard metal is an alloy or encapsulated mixture that is composed of tungsten or tungsten carbide and cobalt (primarily, although the alloys may also contain yttrium, thorium, copper, nickel, iron, or molybdenum). Historically, the respiratory and neurological effects observed in hard metal workers have been attributed to cobalt, not tungsten. However, based on the presence of tungsten oxide fibers in air samples taken at some hard metal facilities and demonstrations that tungsten oxide fibers are capable of generating hydroxyl radicals in human lung cells *in vitro*, it has been suggested that tungsten oxide fibers may contribute to the development of pulmonary fibrosis in hard metal workers.

Limited reports associate tungsten exposure with reproductive and developmental effects such as decreased sperm motility, increased embryotoxicity, and delayed fetal skeletal ossification in animals. However, more detailed accounts of tungsten-induced reproductive and developmental toxicity were not located. Tungsten has been observed to cross the placental barrier and enter the fetus. Dermal or ocular exposure to tungsten may result in localized irritation. No adequate animal data are available to assess the carcinogenic potential of tungsten or tungsten compounds. Tungsten has recently been nominated to the National Toxicology Program (NTP) for toxicological characterization, which includes carcinogenicity testing.

2.3 MINIMAL RISK LEVELS

Inhalation MRLs

No inhalation MRLs were derived for tungsten or tungsten compounds since adequate data were not available for this route of exposure.

Oral MRLs

No oral MRLs were derived for tungsten or tungsten compounds due to a lack of availability of data for this route of exposure. This finding will be evaluated based on a review of several recently translated foreign articles to determine if the data they contain and the scientific method under which they were developed are adequate for MRL derivation.

3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of tungsten. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration 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. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which

major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary 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 in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for tungsten. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the 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.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

3.2.1 Inhalation Exposure

Pulmonary fibrosis, memory and sensory deficits, and increased mortality due to lung cancer have been associated with occupational exposure to dusts generated during the manufacture of malleable tungsten (see Bech 1974; Bech et al. 1962; Coates and Watson 1971; Jordan et al. 1990; Kaplun and Mezentseva 1959; Lasfargues et al. 1994; Mezentseva 1967; Miller et al. 1953; Moulin et al. 1998; Vengerskaya and Salikhodzhaev 1962). High tensile strength tungsten (hard metal) is an alloy that is composed of tungsten carbide and cobalt. Other metals (yttrium, thorium, copper, nickel, iron, or molybdenum) can be included in the alloy to achieve specific metallurgical properties, and some may not actually contain cobalt. The term "hard-metal disease" has been coined to describe pulmonary effects resulting from occupational exposure to hard metal. It is generally believed that the health effects observed in hard metal workers are the result of exposure to cobalt, not tungsten (see Davison et al. 1983; Harding 1950). No information was located regarding potential contributions of other metals present in hard metal. Refer to Section 3.2.1 of the ATSDR Toxicological Profile for Cobalt for detailed information regarding health effects from exposure to cobalt (Agency for Toxic Substances and Disease Registry 2001). It has been suggested that tungsten carbide may increase the solubility of cobalt, effectively increasing cobalt-induced toxicity (Lasfargues et al. 1995; Lison et al. 1995, 1996).

3.2.1.1 Death

No reports were located in which death in humans could be specifically associated with exposure to airborne tungsten or tungsten compounds. Increased mortality has been associated with occupational exposure to dusts containing tungsten carbide and cobalt among hard metal workers. However, the causative agent was considered to have been cobalt, not tungsten carbide (see the ATSDR Toxicological Profile for Cobalt [Agency for Toxic Substances and Disease Registry 2001] for more detailed information).

No reports were located regarding death in animals that could be specifically attributed to inhalation exposure to tungsten or tungsten compounds. However, Lasfargues et al. (1992) found intratracheally-instilled hard metal (tungsten carbide and cobalt alloy) to be more acutely lethal to rats than either tungsten carbide or cobalt alone. It has been suggested that tungsten carbide may increase the solubility of cobalt, effectively increasing cobalt-induced toxicity (Lasfargues et al. 1995; Lison et al. 1995, 1996).

3.2.1.2 Systemic Effects

Available information in humans is limited to occupational exposure to dusts containing tungsten and other substances such as cobalt in the hard metal industry, and reported systemic effects have been associated with cobalt rather than tungsten. Therefore, human data are not included in Table 3-1 and Figure 3-1. A LOAEL for serious effects (pulmonary fibrosis) was identified in a single study of rats exposed to atmospheres containing tungsten carbide during a 5-month period. This LOAEL is recorded in Table 3-1 and plotted in Figure 3-1.

No reports were located in which cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, dermal, or ocular effects were associated with inhalation exposure of humans or animals to tungsten or tungsten compounds.

Respiratory Effects. Respiratory effects were reported in workers who were occupationally exposed to airborne dusts containing tungsten trioxide, tungsten dioxide, metallic tungsten, and tungsten carbide in areas where high tensile strength tungsten was prepared (Mezentseva 1967). Of 54 workers examined, 5 exhibited early radiographic signs of pulmonary fibrosis after having been employed for 2–3 years (3 workers) or 19 or 24 years. Other potentially hazardous substances may have also been present in the workplace air. Respiratory effects associated with occupational exposure to dusts containing tungsten carbide, cobalt, and other metals in the hard metal industry have been associated with cobalt, not tungsten carbide. Refer to the ATSDR Toxicological Profile for Cobalt (Agency for Toxic Substances and Disease Registry 2001), as well as Kerley et al. (1996) and NIOSH (1977) for discussions of respiratory effects associated with the hard metal industry.

Few reports were located regarding respiratory effects in animals. Signs of mild pulmonary fibrosis were noted in rats exposed to atmospheres containing tungsten carbide at a concentration of 600 mg/m^3, 1 hour/day for 5 months (Mezentseva 1967). Other rats exhibited similar signs of pulmonary fibrosis following intratracheal instillation of metallic tungsten, tungsten trioxide, or tungsten carbide and subsequent observations for up to 8 months postinstillation (Mezentseva 1967). Guinea pigs that received 3 weekly doses of tungsten metal dust or tungsten carbide and carbon dust via intratracheal instillation were examined for up to 12 months posttreatment (Delahant 1955; Schepers 1955a, 1955b). Gross histological examinations of the lungs revealed pigmented lung lesions that did not appear to involve lymphoid tissue; the results were not suggestive of pulmonary fibrosis. The lungs of mice exhibited no signs of a fibrotic response following intratracheal instillation of tungsten carbide (Lardot et al. 1998).

Table 3-1 Levels of Significant Exposure to Tungsten - Inhalation

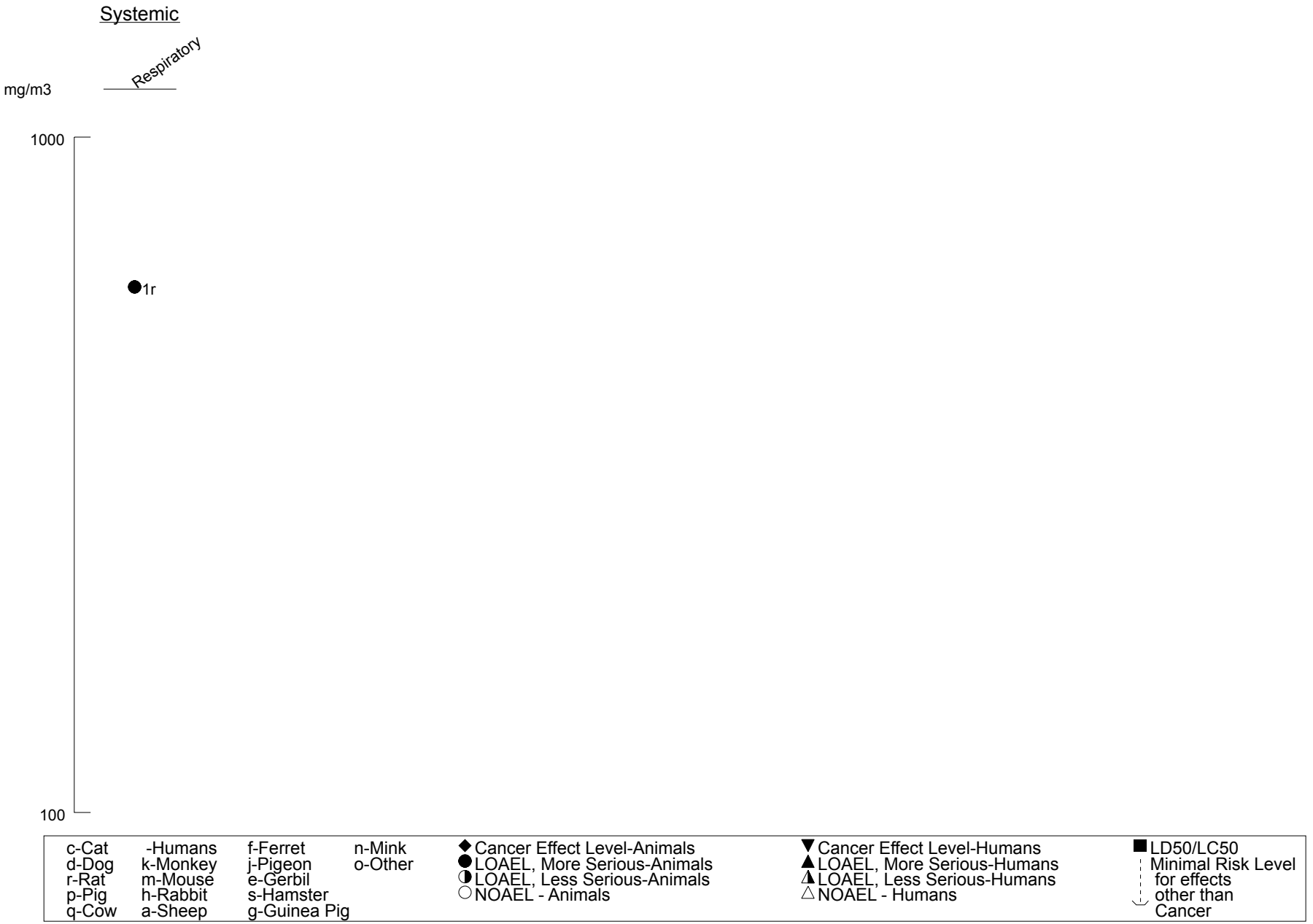
Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m^3)	LOAEL Less Serious (mg/m^3)	LOAEL Serious (mg/m^3)		Reference Chemical Form
	INTERMEDIATE EXPOSURE							
	Systemic							
1	Rat (NS)	5 mo 1hr/d	Resp			600	(pulmonary fibrosis)	Mezentseva 1967 tungsten carbide

a The number corresponds to entries in Figure 3-1

LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; Resp = respiratory

Figure 3-1 Levels of Signicant Exposure to Tungsten - Inhalation

Intermediate (15-364 days)



Lasfargues et al. (1992) reported severe acute pulmonary edema in rats that had received hard metal (tungsten carbide and cobalt alloy) via intratracheal instillation, but not in rats similarly exposed to tungsten carbide or cobalt alone. In a subsequent study of repeated intratracheal instillation (Lasfargues et al. 1995), it was demonstrated that intratracheally-instilled tungsten carbide and cobalt in combination, but not alone, induced interstitial pulmonary fibrosis.

3.2.1.3 Immunological and Lymphoreticular Effects

No reports were located regarding immunological or lymphoreticular effects in humans or animals following inhalation exposure to tungsten or tungsten compounds.

Intratracheal instillation of 250 μg of water-insoluble calcium tungstate crystals (in saline) in mice resulted in a marked inflammatory response characterized by infiltration of leukocytes with cellular peaks at days 1 and 14 postinstillation (Peão et al. 1993). The inflammatory response was likely the result of local irritation rather than an adverse immunological effect.

3.2.1.4 Neurological Effects

Signs of memory and sensory deficits have been reported among workers in the hard metal industry who were exposed to atmospheres of hard metal dusts (Jordan et al. 1990; Kaplun and Mezentseva 1959; Vengerskaya and Salikhodzhaev 1962). Cobalt was the likely causative agent, not tungsten. Refer to the ATSDR Toxicological Profile for Cobalt (Agency for Toxic Substances and Disease Registry 2001) for detailed information regarding cobalt-induced neurological effects. Potential contributions of dust from other metals that may have been present in the workplace air were not assessed.

Information in animals is limited to a single report of a series of inhalation exposures to airborne sodium tungstate powder (Idiatullina 1981). Muzzle scratching and increased activity (interpreted by the author as anxiety manifestations) were noted in male rats continuously exposed to atmospheres containing sodium tungstate powder at concentrations of 100 and 600 mg/m^3 for up to 30 days. Statistically significantly depressed blood cholinesterase activity (magnitude not specified in the available account of the original study) was noted following 18 hours of exposure at a concentration of 600 mg/m^3 and following 720 hours of exposure to a concentration of 10 mg/m^3. In rats exposed to concentrations of 0.5 and 1.0 mg/m^3 for 4 months, blood cholinesterase levels were depressed by 22 and 25%, respectively,

relative to controls, and diffuse sclerosis was noted in brain tissue. These effects were not seen at a lower concentration (0.1 mg/m^3). The low magnitude blood cholinesterase depression renders the results of questionable toxicological significance.

3.2.1.5 Reproductive Effects

No reports were located regarding reproductive effects in humans following inhalation exposure to tungsten or tungsten compounds.

Decreased sperm motility (10–12% lower than controls) was reported in male rats continuously exposed to atmospheres containing sodium tungstate powder for 17 weeks at concentrations of 1.0 and 0.5 mg/m^3, but not at 0.1 mg/m^3 (Idiatullina 1981).

3.2.1.6 Developmental Effects

No reports were located regarding developmental effects in humans or animals following inhalation exposure to tungsten or tungsten compounds.

3.2.1.7 Cancer

No reports were located in which cancer in humans or animals could be associated with inhalation exposure to tungsten or tungsten compounds.

3.2.2 Oral Exposure

The toxicity of ingested tungsten in humans is not known. In an early report, Kruger (1912) reported no adverse effects on patients administered 25–80 g of tungsten powder as a substitute for barium in radiological exams. Nausea, followed by seizure, 24-hour coma, temporary renal failure, and subsequent tubular necrosis and anuria were reported in a male subject who had accidentally consumed tungsten in a mixture of beer and wine (Marquet et al. 1997). However, these effects could not be attributed to the consumption of tungsten per se. The toxicity of orally-administered tungsten has not been widely studied in animals. Available reports implicate reproductive, developmental, and neurological effects as end

points of concern following oral exposure to tungsten (Karantassis 1924; Nadeenko 1966; Nadeenko and Lenchenko 1977; Nadeenko et al. 1977, 1978).

3.2.2.1 Death

No reports were located in which death in humans was associated with oral exposure to tungsten or tungsten compounds.

Acute oral exposure to tungsten does not appear to be a particular toxicity concern, based on acute oral LD_{50} values ranging from 240 to 11,300 mg/kg/day for several soluble tungsten compounds (Table 3-2). Death was reported in guinea pigs following single oral (gavage) administration of sodium tungstate at doses ≥780 mg/kg (Karantassis 1924). Concentrations of 2.0% tungsten (as sodium tungstate), 4% tungsten (as tungstic oxide), or 5.0% tungsten (as ammonium paratungsten), in the daily diet of rats resulted in 100% mortality within 10 days following the initiation of test diet (Kinard and Van de Erve 1941). Diets containing the equivalent of 0.5% tungsten (as sodium tungstate, tungstic oxide, or ammonium paratungstate) resulted in mortality of 3/6 males and 4/6 females, 4/5 males and 5/5 females, and 0/5 males and 0/5 females, respectively. No deaths occurred in rats receiving 0.1% tungsten (as sodium tungstate or tungstic oxide) in the diet for 70 days. In another study, no deaths were reported in rats administered diets containing as much as 10% tungsten metal powder for 70 days (Kinard and Van de Erve 1943). Approximately 15% decreases in longevity were observed in male, but not female, rats administered tungsten (as sodium tungstate) in the drinking water at a concentration of 5 mg/L for life (up to 3 years) (Schroeder and Mitchener 1975a, 1975b).

Available information regarding mortality and LD_{50} values in animals orally exposed to selected tungsten compounds is recorded in Table 3-3 and plotted in Figure 3-2.

3.2.2.2 Systemic Effects

No human data were located in which systemic toxicity could be associated with oral exposure to tungsten or tungsten compounds. Apparent tungsten-induced alterations in body weight (<10% lower than controls) and body weight gains (<20% lower than controls) in animals receiving repeated oral doses of tungsten compounds were not considered to be toxicologically significant in the absence of other

Table 3-2. Oral LD_{50} (mg/kg) Values for Selected Tungsten Compounds

Species	Tungsten oxide	Sodium tungstate	Ammonium-p-tungstate	Sodium phosphotungsten
Mouse	NA	240±13.5[a]	NA	700±79[a]
Rat	840[a]	1,190±129.5[a]	11,300[b]	1,600±201[a]
Rabbit	NA	875[a]	NA	NA
Guinea pig	NA	1,152[a]	NA	NA

[a]Nadeenko 1966
[b]Smyth et al. 1969

LD_{50} = dose of substance causing death in 50% of population; NA = not available

Table 3-3 Levels of Significant Exposure to Tungsten - Oral

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
ACUTE EXPOSURE							
Death							
1	Rat (NS)	Once (NS)				1190 (LD50)	Nadeenko 1966 sodium tungstate
2	Rat	Once				1600 (LD50)	Nadeenko 1966 sodium phosphotungsten
3	Rat (Wistar)	Once (G)				11300 M (LD50)	Smyth et al. 1969 ammonium paratungstate
4	Mouse	Once				240 (LD50)	Nadeenko 1966 sodium tungstate
5	Mouse	Once				700 (LD50)	Nadeenko 1966 sodium phosphotungsten
6	Gn Pig	Once				1152 (LD50)	Nadeenko 1966 sodium tungstate

Table 3-3 Levels of Significant Exposure to Tungsten - Oral (continued)

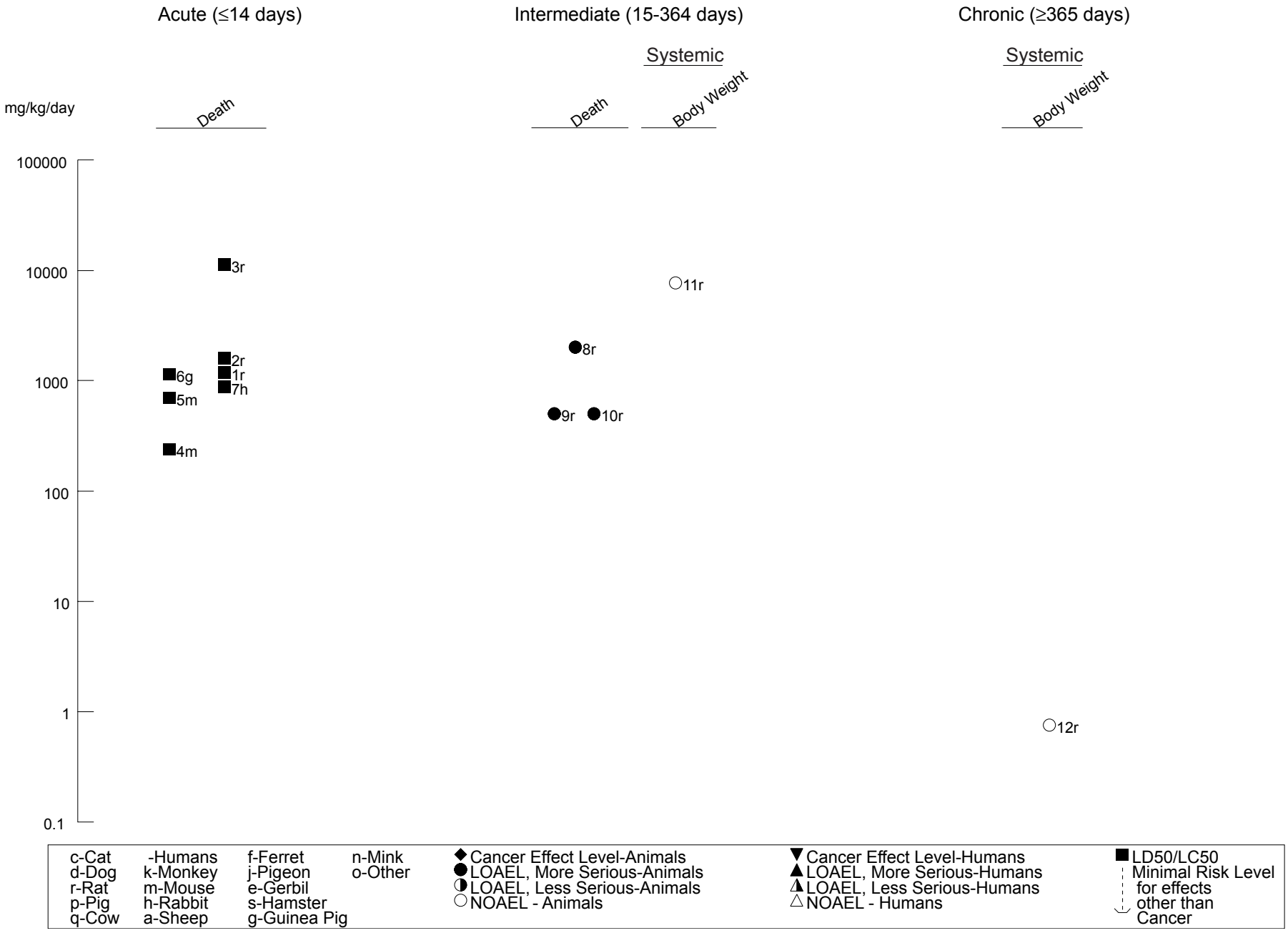
Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)		Reference Chemical Form
7	Rabbit	Once				875	(LD50)	Nadeenko 1966 sodium tungstate
	INTERMEDIATE EXPOSURE							
	Death							
8	Rat (NS)	70 d (F)				2000	(80% mortality)	Kinard and Van de Erve 1941 ammonium paratungstate
9	Rat (NS)	70 d (F)				500	(80% mortality)	Kinard and Van de Erve 1941 tungstic oxide
10	Rat (NS)	70 d (F)				500	(mortality of 3/6 males and 4/6 females)	Kinard and Van de Erve 1941 sodium tungstate
	Systemic							
11	Rat	70 d (F)	Bd Wt	8256 M 7650 F[b]				Kinard and Van de Erve 1943 metallic tungsten
	CHRONIC EXPOSURE							
	Systemic							
12	Rat (Long- Evans)	Lifetime (W)	Bd Wt	0.75 M[b] 1 F				Schroeder and Mitchener 1975a sodium tungstate

a The number corresponds to entries in Figure 3-2

b Differences in levels of health effects and cancer effects between male and females are not indicated in Figure 3-2. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

Bd Wt = body weight; F = female; (F) = feed; LD50 = dose producing 50% death; LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; (NS) = not specified; (W) = drinking water

Figure 3-2. Levels of Significant Exposure to Tungsten - Oral



adverse effects and are not included in Table 3-3 and Figure 3-2. Reliable NOAELs for body weight changes are recorded in Table 3-3 and plotted in Figure 3-2.

No reports were located in which respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, endocrine, dermal, or ocular effects were associated with oral exposure of humans or animals to tungsten or tungsten compounds.

Renal Effects. Available information in humans is restricted to an account of temporary renal failure and subsequent tubular necrosis and anuria in a male subject 1 day following the accidental consumption of tungsten in a mixture of beer and wine that had been poured into the hot barrel of a 155-mm gun (Marquet et al. 1997). The author estimated the absorbed dose of tungsten to be in the range of 5–12 mg/kg. The subject fully recovered.

No information was located regarding renal effects in animals following oral exposure to tungsten or tungsten compounds.

Body Weight Effects. No information was located regarding body weight effects in humans following oral exposure to tungsten or tungsten compounds.

Available information regarding tungsten-induced body weight effects in animals is limited to reports by a single group of investigators (Kinard and Van de Erve 1941, 1943). Reduced body weight gains were noted in rats exposed to sublethal concentrations of tungsten (0.5%, as ammonium paratungstate; 0.1%, as sodium tungstate or tungstic oxide) in the diet for 70 days (Kinard and Van de Erve 1941). Body weight gain in these treated groups ranged from 3.9 to 10.6% lower than respective controls. Weight gain in female rats, administered a diet that included 10% tungsten (as insoluble tungsten metal) for 70 days, was approximately 15.5% less than that of controls; weight gain in similarly dosed male rats was described as "normal" (Kinard and Van de Erve 1941). The authors stated that diets containing 2 or 5% tungsten (as tungsten metal) were "without marked effect" on growth. Statistically significantly increased body weights were noted at some time points in male and female rats administered tungsten (as sodium tungstate) in the drinking water at a concentration of 5 mg/L for a lifetime (Schroeder and Mitchener 1975a). Since the body weights were less than 10% higher than controls and were only seen in males at 180–540 days of treatment and in females at the 360-day examination period, the increased body weight is not considered to be biologically significant.

3.2.2.3 Immunological and Lymphoreticular Effects

No reports were located regarding immunological or lymphoreticular effects in humans or animals following oral exposure to tungsten or tungsten compounds.

3.2.2.4 Neurological Effects

Information in humans is restricted to a single account of nausea, followed by seizure and 24-hour coma in a male subject who had accidentally consumed tungsten in a mixture of beer and wine that had been poured into the hot barrel of a 155-mm gun (Marquet et al. 1997). The author estimated the absorbed dose of tungsten to be in the range of 5–12 mg/kg. The subject fully recovered.

Available early animal data indicate that orally administered tungsten may induce neurological effects. Guinea pigs exhibited clinical signs that included trembling and abnormal locomotory behavior following single oral (gavage) administration of sodium tungstate at ultimately lethal doses ($\geq$780 mg/kg) (Karantassis 1924). Decreased blood cholinesterase activity and impaired conditioned reflexes were reported in rats orally exposed to sodium tungstate at doses in the range of 0.05–5.0 mg/kg/day for 7 months (Nadeenko 1966). Deficiencies in study details render the results of this Russian study of questionable value for purposes of risk assessment.

3.2.2.5 Reproductive Effects

No information was located regarding reproductive effects in humans following oral exposure to tungsten or tungsten compounds.

Information in animals is limited to reports of embryotoxicity in rats following oral administration of an unspecified tungsten compound at dose levels as low as 0.005 mg/kg for up to 8 months before and during pregnancy (Nadeenko and Lenchenko 1977; Nadeenko et al. 1977, 1978). However, the data were poorly presented and the lack of reporting of study details, such as the form of tungsten administered, the specific route of administration, whether the losses were assessed on a per litter basis or per treatment group, and the magnitude of the treatment-related losses, render the reports of questionable value for purposes of risk assessment.

3.2.2.6 Developmental Effects

No information was located regarding developmental effects in humans following oral exposure to tungsten or tungsten compounds.

Information in animals is limited to reports of delayed fetal skeletal ossification following presumed oral administration of an unspecified tungsten compound at dose levels as low as 0.005 mg/kg to pregnant rat dams (Nadeenko and Lenchenko 1977; Nadeenko et al. 1977, 1978). However, the data were poorly presented and the lack of reporting of study details, such as the form of tungsten administered, the specific route of administration, and the magnitude of the treatment-related losses, render the reports of questionable value for purposes of risk assessment.

3.2.2.7 Cancer

No information was located regarding cancer in humans following oral exposure to tungsten or tungsten compounds.

Gross tumor incidences in rats administered tungsten (as sodium tungstate) in the drinking water at a concentration of 5 mg/L for life were similar to those of controls (Schroeder and Mitchener 1975a). Male rats administered sodium tungstate (100 ppm) in the drinking water for 19 or 30 weeks did not exhibit treatment-related evidence of carcinoma in the esophagus or forestomach; nor did sodium tungstate treatment enhance the carcinogenic effect of *N*-nitrososarcosine ethyl ester, a chemical known to induce esophageal cancer in rats (Luo et al. 1983). In a study designed to assess the effect of systemic sulfite on benzo[*a*]pyrene-induced lung carcinoma in rats, Gunnison et al. (1988) administered sodium tungstate to induce sulfite oxidase deficiency, thus increasing systemic sulfite. In this study, sodium tungstate did not statistically significantly affect the initiation of squamous cell carcinoma of the respiratory tract of benzo[*a*]pyrene-treated rats or incidences of mammary gland tumors.

3.2.3 Dermal Exposure

3.2.3.1 Death

No reports were located in which death in humans was associated with dermal exposure to tungsten or tungsten compounds.

Available information in animals was limited to a single report of death in 0/2, 2/2, and 2/2 rabbits following dermal application of a 5% tungsten chloride solution in single doses of 100, 200, and 1,000 mg/kg, respectively (Dow Chemical Company 1982). The results of this study are recorded in Table 3-4.

3.2.3.2 Systemic Effects

No reports were located in which respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, or body weight effects were associated with dermal exposure of humans or animals to tungsten or tungsten compounds.

Dermal Effects. No reports were located in which dermal exposure to tungsten compounds in humans could be associated with dermal effects. Although dermatitis has been reported among employees of the hard metal industry, results of patch testing implicated cobalt, not tungsten (Schwartz et al. 1945; Skog 1963).

In the only available report of dermal effects in animals following dermal exposure to tungsten, single or repeated dermal application of a 5% tungsten chloride solution in rabbits resulted in contact dermatitis (Dow Chemical Company 1982). The results of this study are recorded in Table 3-4.

Ocular Effects. No reports were located in which dermal exposure to tungsten compounds in humans could be associated with ocular effects.

Instillation of a 5% tungsten chloride solution into the rabbit eye resulted in conjunctivitis, iritis, and corneal haziness that resolved within 14 days postinstillation (Dow Chemical 1982). The results of this study are recorded in Table 3-4.

Table 3-4 Levels of Significant Exposure to Tungsten - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL				Reference Chemical Form
				Less Serious		Serious		
ACUTE EXPOSURE								
Other								
Rabbit (NS)				5 Percent (%)	(temporary ocular irritation)			Dow Chemical Company 1982 tungsten chloride
Rabbit (NS)	NS			5 Percent (%)	(contact dermatitis)			Dow Chemical Company 1982 tungsten chloride
Rabbit (NS)	Once					200 mg/kg	(mortality in 2/2 rabbits)	Dow Chemical Company 1982 tungsten chloride

LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; (NS) = not specified

No reports were located regarding the following health effects in humans or animals following dermal exposure to tungsten or tungsten compounds:

3.2.3.3 Immunological and Lymphoreticular Effects

3.2.3.4 Neurological Effects

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

3.2.4 Other Routes of Exposure

Parenteral injection studies that have been performed using laboratory animals were designed to establish lethal doses of tungsten compounds and to assess the efficacy of methods to reduce toxicity (see also Section 3.11). An LD_{50} value of 500 mg/kg was reported for intraperitoneally injected tungsten metal in rats; tungsten carbide was considered to be essentially inert, although dose levels were not included in the report (Fredrick and Bradley 1946). An LD_{50} was between 140 and 160 mg/kg for tungsten (as sodium tungstate) subcutaneously injected into 66-day-old rats; younger rats appeared to be less sensitive (Kinard and Van de Erve 1940). Intramuscular injection of a 10% aqueous solution of sodium tungstate in rats (Sivjakov and Braun 1959) and rabbits (Lusky et al. 1949) resulted in LD_{50} values of 220.6 and 105 mg/kg, respectively.

3.3 GENOTOXICITY

The genotoxic potential of tungsten and tungsten compounds has not been extensively assessed. Sodium tungstate demonstrated mutagenic activity in a bacterial bioluminescence test in *Photobacterium fischeri* (Pf-13) (Ulitzur and Barak 1988). Sodium tungstate induced lambda prophage in *Escherichia coli* WP2s (λ) (Rossman et al. 1984, 1991) and gene conversion at *trp* 5 and reverse mutation at *ilv* 1 in *Saccharomyces cerevisiae* strain D7 (Singh 1983), and increased recombinant frequency in strain DIS13 (Sora et al. 1986). Positive results were obtained for tungstate anion in Chinese hamster lung V79 cells using the HGPRT forward mutation assay (Zelikoff et al. 1986). Tungsten (form not specified) enhanced mutagenic activity in *Salmonella typhimurium* strain TA98 and Ames mixed strains (TA7001-7006) (Miller and Page 1999).

Sodium tungstate did not increase sister chromatid exchanges in human whole blood cultures or cause chromosome aberrations in human lymphocytes or Syrian hamster embryo cells (Larramendy et al. 1981). The chemical did not induce morphological transformation in Syrian hamster cells (DiPaolo and Casto 1979).

Dose- and time-dependent increases in DNA single strand breaks (comet and alkaline elution tests) and micronucleus induction were observed in human peripheral lymphocytes incubated in either tungsten carbide cobalt alloy or cobalt alone, but not in tungsten carbide alone (Anard et al. 1997; Van Goethem 1997). In each of these tests, the genotoxic effect of the tungsten carbide cobalt alloy was greater than that of cobalt alone, which is consistent with a suggestion that physicochemical properties of the alloy may result in increased production of hydroxyl radicals (see also Section 3.5.2).

3.4 TOXICOKINETICS

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

No quantitative data were located concerning absorption of tungsten in humans following inhalation exposure to tungsten or tungsten compounds. However, absorption of airborne tungsten was indicated by a report that tungsten levels in urine, toenails, and hair of workers occupationally exposed to airborne tungsten were higher than those of controls without known inhalation exposure (Nicolaou et al. 1987).

Available animal data, derived primarily from studies that employed radioactive tungsten isotopes that are identical to their respective nonradioactive isotopes with respect to toxicokinetics, demonstrate absorption following exposure to airborne tungsten. Beagle dogs were exposed (nose only) once (duration unspecified) to particulate aerosols of tungstic oxide ($^{181}WO_3$) (Aamodt 1975). Inhaled radioactivity was determined to range from 1.9 to 8 μCi and the inhaled radioactivity exhibited an activity median aerodynamic diameter (AMAD) of 0.7 μm and a geometric standard deviation of 1.5 μm. An estimated 60% of the inhaled radioactivity was deposited in the respiratory tract, approximately half of which was contained in the tracheobronchial and pulmonary regions. These estimates were based on periodic measurements of radioactivity in inspired versus expired air, in the lung region versus the lower body, and in the urine and feces. An estimated 33% of the radioactivity deposited in the lung was absorbed directly into the blood, most of which had entered the blood within the first 10 days following exposure.

Comparison with results of the investigator's ingestion experiment using a single beagle dog indicated that one-fourth of the radioactivity entering the gastrointestinal tract may have been absorbed to the blood. Therefore, about half of the amount that was initially deposited in the lungs, corresponding to about one-third of the inhaled amount, may have eventually been absorbed to blood.

3.4.1.2 Oral Exposure

No quantitative data were located concerning absorption of tungsten in humans following oral exposure to tungsten or tungsten compounds. However, total intake and urinary and fecal excretion of tungsten and other nonessential elements were recorded for four healthy human volunteers given controlled diets for 5 days (Wester 1974). Assuming that the subjects were in tungsten balance, that the intake was primarily via the diet, and that daily urinary excretion of tungsten (approximately 6 μg/day) was proportional to the daily intake (approximately 10 μg/day), approximately 60% of the ingested tungsten appeared to have been absorbed from the gastrointestinal tract. Additional indication of the absorption of ingested tungsten derives from the findings of high concentrations of tungsten in blood, urine, hair, and nail samples of a 19-year-old male who had consumed a mixture of beer and wine that contained a high concentration of tungsten (Marquet et al. 1997). The tungsten concentrations were measured by inductively coupled plasma (ICP) emission-spectrometry, a procedure that did not detect tungsten in samples taken from individuals without known exposure to tungsten at levels above normal background.

Results of animal studies suggest that tungsten is readily absorbed following oral administration of soluble tungsten compounds. In rats, approximately 40% of an orally administered dose of ^{185}W sodium tungstate (Na_2WO_4) was collected in the 24-hour urine (Ballou 1960; Kaye 1968). Approximately 25% of the activity in a single gavage dose of tungstic oxide was excreted in the urine of a single dog (Aamodt 1975), which indicates that tungsten is readily absorbed from the gastrointestinal tract of the dog as well. Poucheret et al. (2000) and LeLamer et al. (2000) assessed the absorption of tungsten (as sodium tungstate) following single oral administration in rats (36 mg sodium tungstate/kg) and dogs (25 mg sodium tungstate/kg) by plotting plasma tungsten concentrations at a number of time points (up to 24 hours) postadministration and comparing the area under the curve (AUC) in each plot to that obtained from species-specific animals that had received single intravenously-administered doses of 8.97 mg sodium tungstate/kg. Using this approach, absorption of tungsten was calculated to approximate 92% in the rat and 65% in the dog. Absorption of tungsten was calculated to approximate 55% during repeated oral dosing of dogs at 5–20 mg sodium tungstate/kg, 3 times/day for 13 weeks (LeLamer et al. 2001).

3.4.1.3 Dermal Exposure

No studies were located regarding absorption of tungsten in humans or animals following dermal exposure to tungsten or tungsten compounds. However, the report of death in rabbits following dermal application of a 5% tungsten chloride solution in single doses of 100–1,000 mg/kg (Dow Chemical Company 1982) indicates that dermal absorption of tungsten occurs to some extent.

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

No reports were located regarding quantifiable distribution of tungsten in humans following inhalation exposure to tungsten or tungsten compounds. However, when compared to controls without known occupational exposure to tungsten, higher levels of tungsten in hair and nails of workers occupationally exposed to airborne tungsten serves as indication that inhaled tungsten may be distributed to these sites (Nicolaou et al. 1987).

Beagle dogs were exposed (nose only) once (duration unspecified) to particulate aerosols of tungstic oxide ($^{181}WO_3$) (Aamodt 1975). Inhaled radioactivity was determined to range from 1.9 to 8 μCi, and the inhaled radioactivity exhibited a mean aerodynamic diameter (AMAD) of 0.7 μm and a geometric standard deviation of 1.5 μm. Approximately 70% of the initial tungsten lung burden, which was estimated to have been approximately 60% of the inhaled radioactivity, was removed with a half-time of 4 hours. Another 20–25% was removed with a half-time of 20 hours, and approximately 5% with a half-time of 6.3 days. A small amount of tungsten may have been retained by the lung for months. Approximately 33% of the tungsten that was removed from the lung entered the blood directly. An estimated 66% was transported upwards via mucociliary action and swallowed, most of which was subsequently excreted in the feces. At sacrifice (approximately 165 days postexposure), the average body burden calculated from organ and tissue samples was 0.017 (1.7%) of the inhaled activity. The highest concentrations were in the lungs and kidneys. Radioactivity measured in bone, gall bladder, liver, and spleen was approximately 10-fold lower than that of lungs and kidneys. Measurable activity was also found in decreasing concentration in testes, pancreas, large intestine, small intestine, diaphragm, stomach, heart, and skeletal muscle, respectively. In terms of total activity in individual organs and tissues, activity was highest in bone (37% of the body burden at sacrifice), followed by lung (31%), kidneys (15%), liver (9.7%), and skeletal muscle (5.7%).

3.4.2.2 Oral Exposure

No reports were located regarding quantifiable distribution of tungsten in humans following oral exposure to tungsten or tungsten compounds. However, findings of measurable levels of tungsten in blood, urine, hair, and nail samples, taken from a 19-year-old male who had consumed a mixture of beer and wine that contained a high concentration of tungsten (Marquet et al. 1997), indicated that ingested tungsten is absorbed by the blood and distributed systemically. The presence of tungsten in the urine of subjects who voluntarily consumed diets that were supplemented with tungsten is further indication that ingested tungsten is distributed systemically (Wester 1974).

Results of animal studies indicate that orally administered tungsten (in soluble form) rapidly enters the blood and is distributed via systemic circulation. In rats, most of the radioactivity in an initial oral (gavage) dose of sodium tungstate (activity of 34.3 μCi) had been eliminated in the first 24 hours postadministration (Ballou 1960). However, approximately 2% of the initial radioactivity was retained. On day 1 postadministration, the highest concentrations of radioactivity were measured in the gastrointestinal tract, followed by spleen, kidneys, pelt, and skeleton. Measurable concentrations were also noted in liver > ovaries > pancreas > lung > heart > blood > fat > muscle. At 102 days postadministration, the highest concentrations of retained radioactivity were in the spleen and skeleton. Total skeletal deposition was about 0.4% of the administered dose.

Similar results were reported by Kaye (1968). Rats were administered single gavage doses of solutions containing radiotungsten (^{187}W or ^{185}W) as tungstate. Distribution and elimination of radioactivity was examined for 72 hours (^{187}W) or 254 days (^{185}W) postadministration. During the first 24 hours following dosing, virtually all of the radioactivity measured in the blood was associated with the plasma portion. During the next 2 days of measurements, radioactivity appeared in the cellular portion and accounted for approximately two-thirds of the radioactivity in the blood 72 hours following dosing, at which time, approximately 97% of the initially administered dose of radiotungsten had been eliminated from the body. During the first week after dosing, highest concentrations of radiotungsten in soft tissues were observed in spleen, hair, kidney, uterus, liver, prostate, and ovary. After 100 days, >99% of the remaining total body burden (approximately 0.4% of the administered dose) was retained in bone.

Results of an earlier rat study (Kinard and Aull 1945) also indicated that bone and spleen retained the highest concentrations of tungsten following dietary administration of tungsten (as tungstic oxide, sodium tungstate, ammonium paratungstate, or tungsten metal) for 100 days.

3.4.2.3 Dermal Exposure

No studies were located regarding distribution of tungsten in humans or animals following dermal exposure to tungsten or tungsten compounds. However, a report of death in rabbits following a single dermal application of a 5% tungsten chloride solution (Dow Chemical Company 1982) is evidence of systemic distribution of dermally-applied tungsten.

3.4.2.4 Other Routes of Exposure

Intravenous injection studies of radiotungsten ($Na_2{}^{181}W0_4$) support the results of inhalation and oral studies (Ando et al. 1989; Wase 1955; Wide et al. 1986). Three hours postadministration, levels of radiotungsten in rats were as follows: kidney > bone > liver >lung > adrenal > spleen > pancreas > blood > thymus > cardiac muscle > skeletal muscle > brain (Ando et al. 1989). At 48 hours postadministration, the highest levels of radiotungsten were found in bone > kidney > lung and liver > spleen. Lesser amounts were noted in the other examined tissues and organs. Eight hours following intraperitoneal injection of ^{185}W (as $K_2{}^{185}WO_4$) in mice, relative concentrations of radioactivity were: bone > gastrointestinal tract > spleen > kidney > red blood cells > heart > lung > liver > plasma > brain (Wase 1955). After 48 hours postadministration, nearly all of the measurable radioactivity was in the bone.

Wide et al. (1986) demonstrated that intravenously injected tungstate (^{185}W) readily crossed the placenta of pregnant rats and was distributed to the fetus. Embryonic uptake was greater in dams injected at later stages of gestation (day 17) as opposed to earlier stages (day 8 or 12). Radiotungsten accumulated in yolk sac epithelium at all examined gestational stages. The highest level of fetal retention was noted in the skeleton.

3.4.3 Metabolism

Tungsten ion in the body is not known to be metabolized. It has been postulated that tungsten may preferentially occupy enzyme sites normally reserved for the essential element, molybdenum, because sodium tungstate has been shown to antagonize the normal metabolic action of molybdate in its role as cofactor for the enzymes xanthanine dehydrogenase (Higgins et al. 1956a, 1956b), sulfite oxidase, and aldehyde oxidase (Johnson and Rajagopalan 1974), and xanthine oxidase secretion to milk (Owen and Proudfoot 1968) in animal systems. See Section 3.5.2 for detailed information regarding mechanisms of tungsten-induced toxicity.

3.4.4 Elimination and Excretion

Elimination and excretion of tungsten is discussed without subdividing data according to route of exposure. Once tungsten has been systemically distributed following inhalation, oral, or dermal exposure or parenteral injection, the pattern of elimination is similar across exposure routes.

Information concerning elimination and excretion of tungsten in humans is limited to findings of measurable amounts of tungsten in urine of individuals exposed to tungsten either in the workplace air (see Barborik 1972; Nicolaou et al. 1987) or by controlled (Wester 1974) or accidental (Marquet et al. 1997) ingestion of tungsten.

Inhalation, oral, and parenteral injection studies in laboratory animals all indicate that absorbed tungsten is rapidly eliminated from the blood and quickly excreted in large quantities in the urine. Combined urinary and fecal excretion of radiotungsten from dogs following inhalation exposure to particulate aerosols of $^{181}WO_3$ was described by three exponential components (Aamodt 1975). Approximately 90% of the inhaled radioactivity was removed with a biological half-time of about 14 hours; 6% with a half-time of 5.8 days, and 4% with a half-time of 63 days. The average urine to fecal ratio was 1.14 for the 100 days of postexposure measurements, including the portion of tungsten that entered the blood directly from the lungs (approximately 33% of the deposited dose) as well as that which was deposited in the gastrointestinal tract via mucociliary clearance (approximately 66% of the initial lung burden).

Radiotungsten was rapidly excreted from rats following oral dosing (Kaye 1968). In a study of rats administered single gavage doses of ^{185}W and followed for 72 hours, approximately 40% of the administered dose of radiotungsten had been eliminated in the urine in the first 12 hours postadministration; an additional 3% was eliminated during the subsequent 60 hours. The initial rate of fecal excretion was lower than that of urinary excretion; however, by 72 hours, fecal excretion had accounted for approximately 53% of the administered dose. Thus, 72-hour urinary and fecal excretion accounted for 97% of the administered dose. Other rats were similarly administered ^{185}W and followed for up to 254 days. During the first 3 days following dosing, approximately 36 and 39% of the administered dose had been recovered in the urine and feces, respectively. By day 33 postadministration, radiotungsten could no longer be detected in the feces. Trace amounts of radiotungsten were still detected in urine analyses conducted until day 191 and correlated with slow elimination of ^{185}W from bone. In

dairy cows that were orally administered radiotungsten, approximately 0.4% of the administered dose was recovered in the milk during the first 84 hours postadministration (Mullen et al. 1976).

Following intravenous injection of dogs with ^{181}W (as sodium tungstate), elimination from the blood was rapid (Aamodt 1973). By 24 hours, 91% of the injected radioactivity had been excreted in the urine. An initial urinary to fecal ratio of 49 on day 1 was reduced to a constant value of 38 by day 7.

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al. 1987; Andersen and Krishnan 1994). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic

equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) is adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

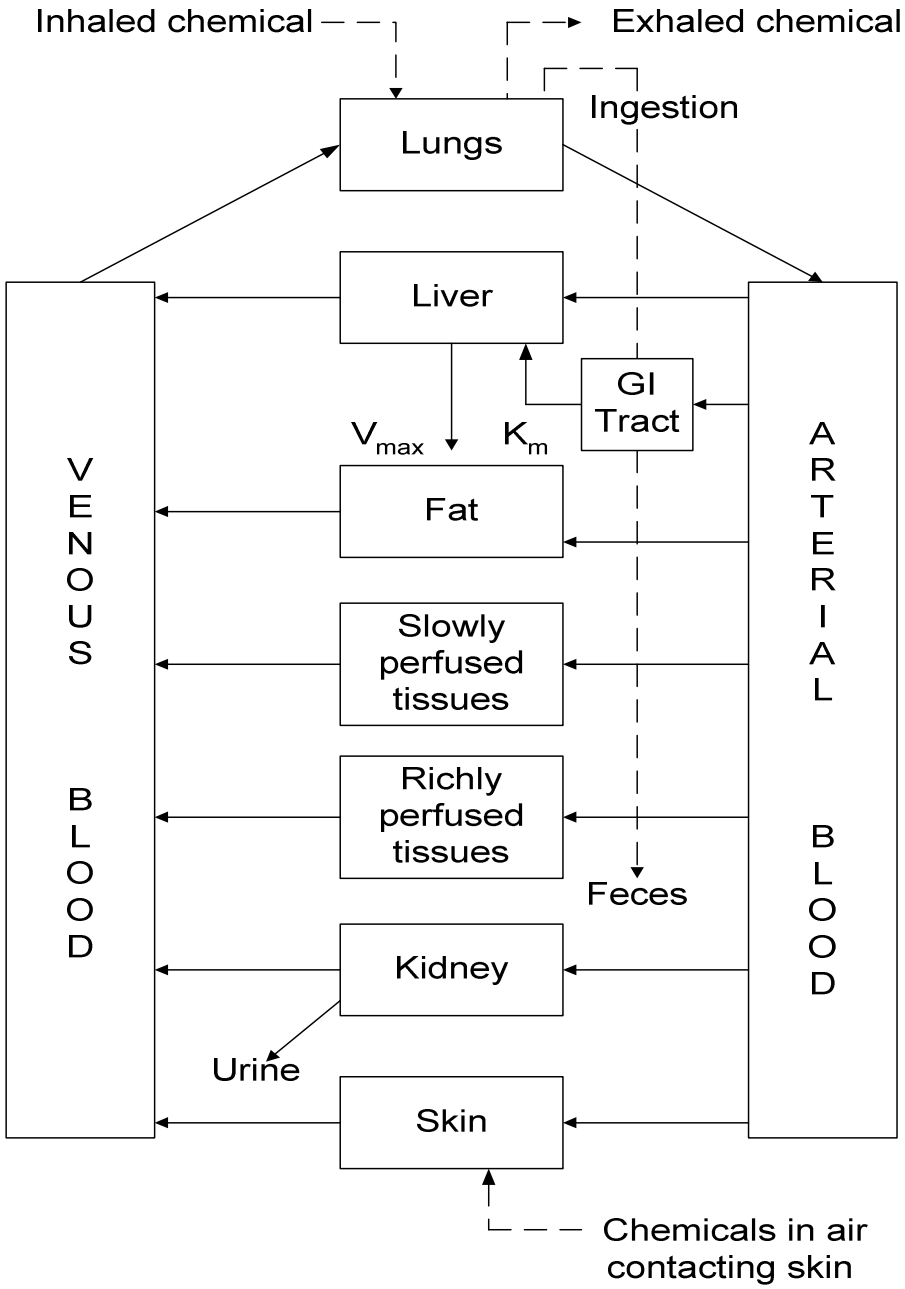
PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-3 shows a conceptualized representation of a PBPK model.

International Commission for Radiological Protection (ICRP 1981) Biokinetic Model for Tungsten

The ICRP's modular approach to biokinetic modeling.

In ICRP documents addressing occupational or environmental exposures to radionuclides, the biokinetic model for an element consists of three submodels: a respiratory tract model, a gastrointestinal tract model, and an element-specific systemic biokinetic model. For a given element, the generic respiratory tract model is used to describe the deposition and retention of inhaled material in the respiratory tract and subsequent clearance to blood or the gastrointestinal tract via mucociliary transport and swallowing. The generic gastrointestinal tract model is used to describe the movement of swallowed or endogenously secreted material through the stomach and intestines, and, together with an element-specific gastrointestinal absorption fraction (f1 value), to describe the rate and extent of absorption of the element

Figure 3-3. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

to blood. An element-specific systemic biokinetic model is used to describe the time-dependent distribution and excretion of the element after its absorption into blood.

The ICRP's gastrointestinal model (ICRP 1979) as applied to tungsten (ICRP 1981).

The ICRP's generic gastrointestinal tract model divides the gastrointestinal contents into stomach (S), small intestine (SI), upper large intestine (ULI), and lower large intestine (LLI). Material moves from S to SI at the rate of 24 day^{-1}, from SI to ULI at 6 day^{-1}, from ULI to LLI at 1.8 day^{-1}, and from LLI to feces at 1 day^{-1}. Absorption to blood is represented as transfer from SI to blood. In the absence of radioactive decay, the fraction f_1 of the ingested element moves from SI to blood and the fraction $1-f_1$ moves from SI to ULI. The transfer coefficient from SI to blood is $6f_1 / (1-f_1)$ day^{-1}. An absorption fraction f_1 of 0.3 is applied to compounds of tungsten other than tungstic acid, for which an absorption fraction of 0.1 is used.

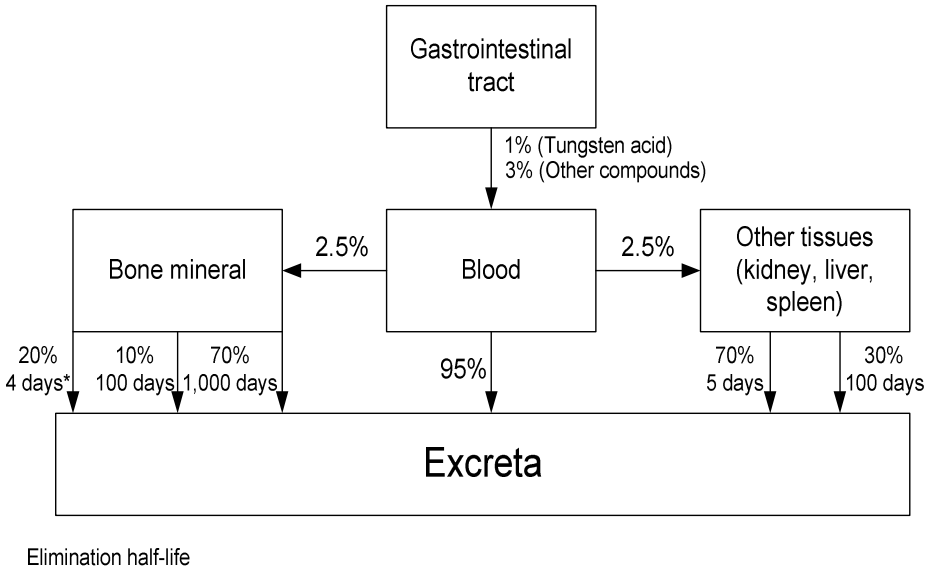
The ICRP's respiratory model (ICRP 1994a) as applied to tungsten (ICRP 1995).

The ICRP uses a generic respiratory model (ICRP 1994a) to describe deposition and retention of inhaled elements in the respiratory tract, absorption to blood, and transfer to the stomach via movement up the tracheobronchial tree in mucus and subsequent swallowing. The kinetics of swallowed activity is described by the gastrointestinal tract model summarized above. Elements or specific compounds of elements inhaled in particulate form are assigned to one of three "absorption types" representing the rate of transfer of material from the lungs to blood, which in turn is related to the rate of dissolution of the material in the respiratory tract. The three absorption types are Type F, representing fast absorption; Type M, representing moderately slow absorption; and Type S, representing slow absorption. There are numerous parameter values associated with each absorption type; these will not be listed here. Compounds of tungsten are assumed to be dissolved fairly rapidly in the respiratory tract and, thus, are assigned to Type F (ICRP 1994b).

The ICRP's systemic biokinetic model for tungsten (ICRP 1981).

The ICRP uses an element-specific systemic biokinetic models to describe the kinetics of the element after its absorption to blood from the respiratory tract or gastrointestinal tract, or entry from wounds or direct injection into blood. The ICRP's current systemic biokinetic model for tungsten (ICRP 1981) was developed in the 1970s. The model (Figure 3-4) consists of exponential curve fits to selected data on the relatively short-term behavior of tungsten in dogs, goats, and rats. In the development of the model, no attempt was made to reflect the physiological processes that control the biokinetics of tungsten or to

Figure 3-4. ICRP (1981, 2001) Biokinetics Model for Tungsten



depict actual paths of movement of this element in the body. Absorbed tungsten is assumed to enter the blood, from which 95% immediately transfers to excreta by unspecified routes, 2.5% transfers to bone mineral, 1% transfers to kidney, 1% transfers to liver, and 0.5% transfers to spleen. Tungsten in bone is removed in excretion with half-times of 4 days (20%), 100 days (10%), and 1,000 days (70%). Tungsten in any other tissue is removed to excretion with half-times of 5 days (70%) and 100 days (30%).

Validation of the model.

The extent to which the ICRP model has been validated is not described in ICRP (1981).

Risk assessment.

The model has been used to establish radiation dose equivalents (Sv/Bq) of ingested and inhaled radioactive tungsten isotopes for ages 1 day to 50 years (ICRP 2001).

Target tissues.

The model is designed to calculate intake limits for radioactive tungsten, based on radiation dose to all major organs, including the bone surfaces, bone marrow, and soft tissues.

Species extrapolation.

The model is designed for applications to human dosimetry and cannot be applied to other species without modification.

Interroute extrapolation.

The ICRP's systemic biokinetic model for tungsten can be applied to any route of exposure (e.g., from the respiratory or GI tract, wounds, through the skin, or via intravenous injection), provided information is available on the time-course of entry of tungsten into blood.

Leggett (1997) Model of the Biokinetics of Absorbed Tungsten

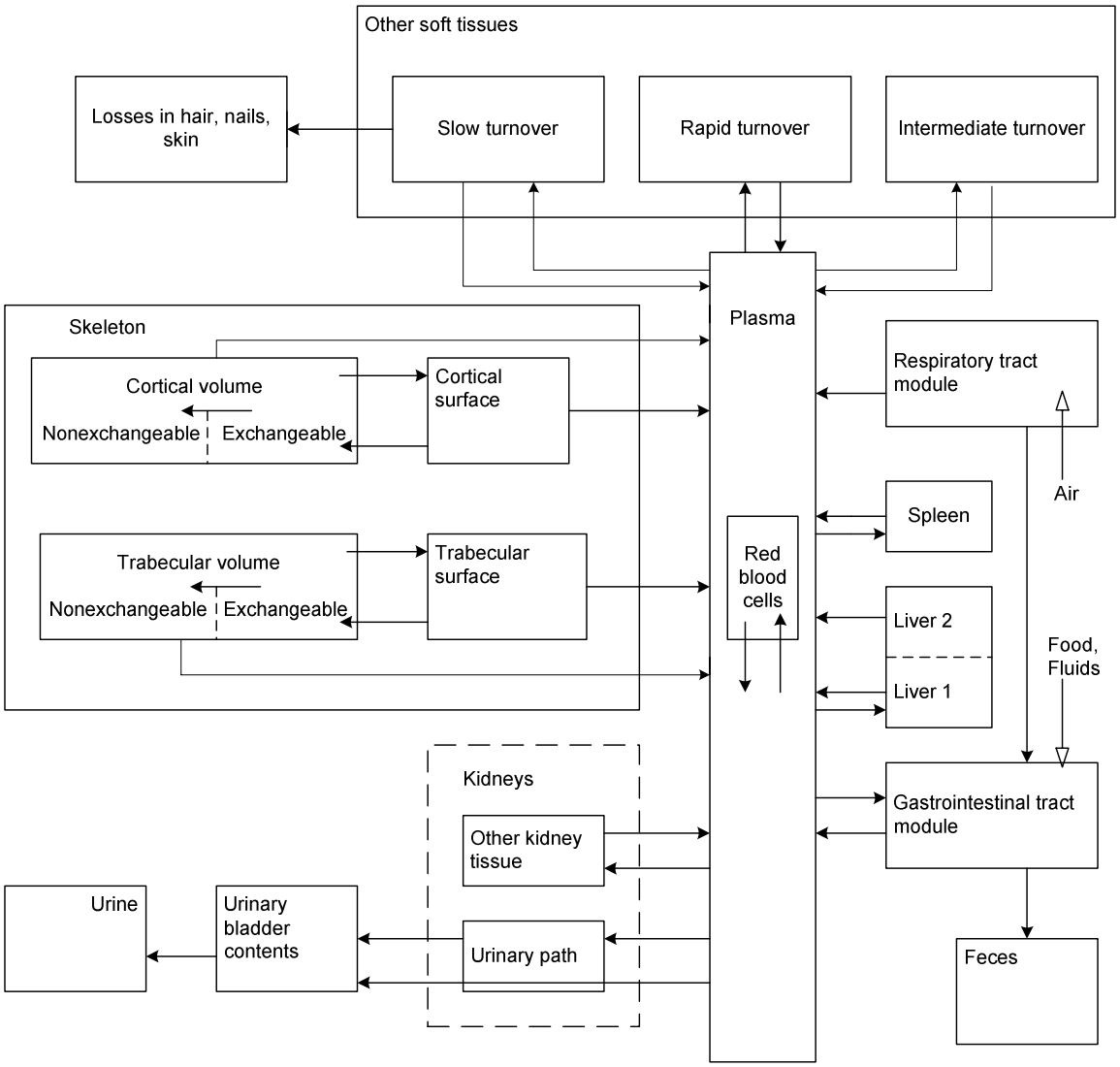
Description of the model.

Leggett (1997) developed a compartmental model of the biokinetics of absorbed tungsten in adult humans that can be linked to the ICRP's gastrointestinal tract model (ICRP 1979, 1981) or respiratory model (ICRP 1994). The model differs considerably from the ICRP's systemic biokinetic for tungsten with regard to structure, basis for parameter values, and predicted retention of tungsten in tissues. The model structure (Figure 3-5)) is intended to depict physiologically realistic directions of movement of tungsten in the human body, including the systemic redistribution of tungsten that enters blood after removal from tissues. Model parameters are based on results of biokinetic studies of tungsten in dogs, swine, sheep, goats, cows, and rodents. Although tungsten biokinetics has been studied more frequently in rats than other species, data for rats were given low weight in selection of most parameter values because of known qualitative differences between rats and humans in the handling of molybdenum, a chemical and physiological analogue of tungsten. It is suspected that membrane transport may not distinguish between analogous compounds of tungsten and molybdenum, although biokinetic differences between tungsten and molybdenum arise, probably because molybdenum compounds are more easily reduced in biological systems (Callis and Wentworth 1977). The species differences recognized for molybdenum may apply to tungsten as well, as suggested by the much faster excretion of tungsten by rats than other studied species and apparent differences in the distribution of retained tungsten. On the other hand, some aspects of the biokinetics of tungsten or molybdenum, including long-term skeletal retention due to substitution of tungstate or molybdate for phosphate in bone, are expected to be independent of species.

The structure of the model for tungsten (Figure 3-5)) is essentially the same as that applied in ICRP Publication 69 (1995) to a set of "bone-volume-seeking" elements, including calcium, strontium, barium, radium, lead, and uranium. It is assumed that the kinetics of tungsten that deposits in bone can be related to the kinetics of the major components of bone mineral, calcium, and phosphorus.

Transport of tungsten between compartments is assumed to follow first-order kinetics. Three compartments are used to describe the kinetics of circulating tungsten: (1) blood plasma, (2) red blood cells, and (3) a rapid-turnover soft-tissue compartment representing extracellular fluids. The rapid-turnover soft-tissue compartment is used to depict an early build-up of tungsten in extravascular spaces followed by relatively rapid feedback to blood. The total transfer rate from plasma to all destinations is set at 16.64 day^{-1}, corresponding to a removal half-time of 1 hour. The rapid-turnover soft-tissue compartment receives 30% of tungsten leaving plasma and returns tungsten to plasma with a half-

Figure 3-5. Leggett (1997) Biokinetics Model for Tungsten



Adapted from Leggett 1997

time of 2 hours. The division of tungsten leaving the circulation, defined as atoms moving from plasma to compartments other than rapid-turnover soft-tissues, is as follows: 75% to the urinary bladder contents; 5% to kidney tissue; 5% to the contents of the upper large intestine (representing all secretions into the gastrointestinal tract); 4% to liver; 8% to bone surfaces; 2.5% to other soft tissues; and 0.5% to red blood cells. The assigned removal half-times from the various compartments within these tissues vary from 1 day (from bone surfaces) to about 23 years (from cortical bone volume). Tungsten removed from the skeleton, certain kidney tissue, liver tissue, remaining soft tissues, and red blood cells is assigned to plasma and redistributed to excretion pathways and tissues in the same ratio as the initial input into plasma. Most of the tungsten removed from kidney tissue is assigned to the urinary bladder contents.

Bone is divided into cortical and trabecular portions and each of these is further divided into a bone surface compartment and exchangeable and nonexchangeable bone volume compartments. Approximately 55% of tungsten entering the skeleton is assigned to trabecular surfaces and 45% to cortical surfaces. Tungsten is removed from bone surface with a half-time of 1 day, with 5/6 returning to plasma and 1/6 entering the corresponding exchangeable bone volume compartment. It is removed from exchangeable bone volume with a half-time of 100 days, with 60% assigned to the corresponding nonexchangeable bone volume compartment and 40% to the corresponding bone surface compartment. Removal from nonexchangeable bone to plasma occurs at the rate of bone turnover, estimated as 0.03 $year^{-1}$ for cortical bone (half-time of ~23 years) and 0.18 $years^{-1}$ for trabecular bone (half-time approximately 4 year).

The model predicts a rapid decline in body burden of tungsten after cessation of exposure; approximately 15% of the burden remains after 1 day, 5% after 1 week, 3% after 1 month, 1.6% after 1 year, and 0.4% after 10 years. The slowest component of the decline represents stores in bone volume; therefore, over time, the fraction of the body burden associated with bone increases to 60% after 1 year and 90% after 4 years. Steady state in soft tissue is predicted after approximately 300–500 days of continuous exposure, whereas, bone continues to accumulate tungsten with chronic exposure.

Validation of the model.

An evaluation of the extent to which the model has been validated was not located. Predictions from the model were compared to those from the ICRP (1981) model (Leggett 1997). Over the first few years after intake, the two models yield reasonably consistent predictions of total-body retention, but noticeably different predictions of retention in specific tissues. For example, the ratio of predicted retention values, ICRP model:Leggett model, at 1 day after acute uptake of tungsten to blood is 0.75 for the total body, but

0.44 for bone or kidney, 0.28 for liver, and 8.5 for spleen. For times greater than a few years after intake, the ICRP model predicts considerably faster decline of activity in all tissues, with the ratio ICRP model:Leggett model at 10,000 days after acute intake being <0.01 for total body or bone retention and <0.001 for retention in all other tissues. Differences in predictions of the two models result in part from differences in the databases considered, in that the ICRP restricted attention to specific data sets and relied heavily on data for rats, which were generally given low weight in the model of Leggett. Predictive differences also arise from differences in the method of extrapolation to times beyond the periods of observation of tungsten retention in laboratory animals. For example, in the ICRP model, a removal half-time from bone of 1,000 days is arbitrarily applied to represent "a very long-term component of retention in the skeleton" (ICRP 1981). In the Leggett model, long-term removal of tungsten from bone is assumed to occur at the rate at which human bone is remodeled.

Risk assessment.

The extent to which the model has been applied to risk assessment is not described in Leggett (1997). The model is configured to be applicable for estimation of time-integrated target tissue doses, blood tungsten levels, and tungsten excretion.

Target tissues.

The model output includes tungsten levels in bone, blood, kidney, liver, other soft tissues, and plasma.

Species extrapolation.

Parameter values of the model were derived for adult humans. The model structure is applicable to other mammalian species, but application to other species would require the derivation of appropriate parameter values based on species-specific information.

Interroute extrapolation.

The Leggett systemic biokinetic model for tungsten can be applied to any route of exposure (e.g., from the respiratory or gastrointestinal tract, wounds, through the skin, or via intravenous injection), provided information is available on the time-course of entry of tungsten into blood.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Absorption. Absorption of inhaled tungsten has been demonstrated in dogs (Aamodt 1975). Approximately one-third of a dose of radiotungsten ($^{181}WO_3$) that was deposited in the respiratory tract was transferred to the blood. Based on relatively rapid clearance of a portion of the deposited activity from the lungs (70% was cleared with a half-time of 4 hours), diffusion may account for at least a portion of the dose entering the blood. Experimental data also indicate that tungsten particles may be dissolved within alveolar macrophages (De Sousa Pereira et al. 1992; Grande et al. 1990; Peão et al. 1993) and transported to the lymphatic system (Águas et al. 1991; Grande et al. 1990). The relative solubility of a given tungsten compound also likely dictates the degree and rate of absorption. At least a portion of tungsten inhaled as hard metal dust may be retained in lung tissue for an extended period (Cugell et al. 1990; Edel et al. 1990).

Ingested tungsten appears to be largely absorbed from the lower ileum, based on results of an *in vitro* study using the rat small intestine (Cardin and Mason 1976). Results of both *in vitro* and *in vivo* studies in rats indicate that gastrointestinal absorption and transport of tungsten probably occurs via the same pathways employed by the essential element molybdenum (Cardin and Mason 1976; Johnson and Rajagopalan 1974; Johnson et al. 1974a, 1974b). The results further indicate that a transport system common to molybdenum and tungsten is subject to competitive inhibition.

No information was located regarding mechanisms involved in absorption of tungsten through the skin. However, a report of death in rabbits following a single dermal application of a 5% tungsten chloride solution (Dow Chemical Company 1982) is evidence of absorption and systemic distribution of dermally-applied tungsten.

Distribution. Absorbed tungsten is rapidly distributed throughout the body and quickly eliminated predominantly via the urine. Mechanisms involved in the distribution of absorbed tungsten are not currently understood. However, rapid distribution via the blood and elimination via the kidney serve as indication that distribution does not likely include major binding to cellular components or proteins in blood. Retention of tungstate by the liver may be related to the findings that tungsten inhibits the binding of the essential element molybdenum to selected liver proteins (Johnson and Rajagopalan 1974). Retention of tungsten in bone has led to the suggestion that tungstate anions interact with calcium, thereby forming the relatively insoluble calcium tungstate (Wase 1956). In physiological systems such as

cells and blood, molecules binding anionic forms of tungsten might release these anions to water in exchange for dissolved phosphate ion, for which they may have greater affinity, as suggested by Wide et al. (1986).

Excretion. Inhalation, oral, and parenteral injection studies in laboratory animals all indicate that absorbed tungsten is rapidly eliminated from the blood and quickly excreted in large quantities in the urine (Aamodt 1973, 1975; Kaye 1968). Specific mechanisms involved in the excretion of tungsten were not identified in available reports.

3.5.2 Mechanisms of Toxicity

Specific mechanisms of tungsten-induced toxicity have not been elucidated. Pulmonary fibrosis in hard metal workers exposed to dusts containing tungsten carbide and cobalt has been historically attributed to the presence of cobalt, not tungsten (see Davison et al. 1983; Harding 1950). Based on results of studies in which pulmonary fibrosis was induced in rats following intratracheal instillation of tungsten carbide and cobalt in combination, but not in rats exposed to tungsten carbide or cobalt alone (Lasfargues et al. 1995), it has been proposed that tungsten carbide, a relatively good conductor of electrons, may facilitate the oxidation of cobalt metal to ionic cobalt, which could increase both the solubility of cobalt and the generation of active oxygen species (Lasfargues et al. 1995; Lison et al. 1995). *In vitro* evidence for this mechanism includes the ability of hard metal particles, but neither cobalt nor tungsten carbide alone, to generate oxidant species and cause lipid peroxidation (Lison et al. 1995; Zanetti and Fubini 1997). Hard metal particles have also been shown to increase the levels of inducible nitric oxide synthase (iNOS); the gene for iNOS is responsive to oxidant stress (Rengasamy et al. 1999).

Leanderson and Sahle (1995) demonstrated that respirable tungsten oxide fibers, which were measured in the air of hard metal industries (80% of the fibers were ≤0.3 μm in diameter) (Sahle 1992; Sahle et al. 1994), are capable of generating hydroxyl radicals in human lung cells *in vitro*, and that these fibers were more cytotoxic than crocidolite asbestos. Generation of hydroxyl radicals might contribute toward the development of pulmonary fibrosis in individuals occupationally exposed to fibrous tungsten oxide in the hard metal industry.

In animals administered high levels of tungsten in combination with low dietary levels of molybdenum, the competitive agonistic properties of the two metals can be manifested by reduced levels of molybdenum and decreased activity of enzymes such as xanthine oxidase, sulfite oxidase and aldehyde

oxidase, which normally incorporate molybdenum as a metal carrier (De Renzo 1954; Higgins et al. 1956a, 1956b; Johnson and Rajagopalan 1974; Johnson et al. 1974). Although these effects can be observed following exposure to elevated levels of tungsten, only very small amounts of supplemental molybdenum are required to reverse these tungsten-induced effects. The competitive agonistic properties of tungsten and molybdenum have not been associated with any observable signs of toxicity.

3.5.3 Animal-to-Human Extrapolations

No data were located concerning major interspecies differences in pharmacokinetics or health effects associated with exposure to tungsten or tungsten compounds. However, the rat exhibits a remarkably low requirement for molybdenum, relative to other animal species (Higgins et al. 1956b). The apparently low dietary requirement of molybdenum in the rat, as well as the competitive agonistic properties of molybdenum and tungsten and their chemical similarities, is suggestive evidence of species-specific differences in the biokinetics of tungsten.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as endocrine disruptors. However, appropriate terminology to describe such effects remains controversial. The terminology endocrine disruptors, initially used by Colborn and Clement (1992), was also used in 1996 when Congress mandated the Environmental Protection Agency (EPA) to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), which in 1998 completed its deliberations and made recommendations to EPA concerning endocrine disruptors. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as hormonally active agents. The terminology endocrine modulators has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et

al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No information was located regarding the potential of tungsten or tungsten compounds to disrupt endocrine function.

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6 Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to

body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

No information was located regarding age-related differences in pharmacokinetics or toxicity of tungsten or tungsten compounds in humans. In one animal study, increased embryonic uptake of tungsten was observed via rat dams administered tungstate (^{185}W) intravenously during late gestation (day 17) compared to earlier treatment (gestation days 8 or 12) (Wide et al. 1986). Both pre- and post-implantation losses and delayed fetal skeletal ossification were reported in rats following oral administration of tungsten before and during pregnancy (Nadeenko and Lenchenko 1977; Nadeenko et al. 1977, 1978). However, the data were poorly presented and the lack of reporting of study details, such as the form of tungsten administered, the specific route of administration, and the magnitude of treatment-related losses, renders the reports of questionable value for purposes of health risk assessment. Particular sensitivity to tungsten during fetal development and postnatal periods of nursing may be of concern since

absorption of tungsten in pregnant animals can result in the accumulation of tungsten in fetal tissues (Wide et al. 1986), and tungsten can enter the milk of tungsten-exposed animals (Mullen et al. 1976). However, no information was located regarding the ability of tungsten to cross the placenta or enter the breast milk of humans.

3.8 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).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. 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(s) or cell(s) 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(s), 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 substance (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 samples can be 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 tungsten and tungsten compounds are discussed in Section 3.8.1.

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 not often substance specific. They also may not be directly

adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by tungsten and tungsten compounds are discussed in Section 3.8.2.

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 substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10 "Populations That Are Unusually Susceptible".

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Tungsten and Tungsten Compounds

The presence of tungsten in the blood, urine, or feces serves as a biomarker of exposure to tungsten or tungsten compounds. Levels in these media may be used in conjunction with biokinetic models to estimate previous exposure levels.

3.8.2 Biomarkers Used to Characterize Effects Caused by Tungsten and Tungsten Compounds

Biomarkers of effect for tungsten or tungsten compounds were not identified in available literature.

3.9 INTERACTIONS WITH OTHER CHEMICALS

No information was located concerning the potential for tungsten or tungsten compounds to interact with other chemicals and thereby potentiate resulting adverse effects. Hard metal, consisting of tungsten carbide and cobalt, has been shown to present a more significant health concern than either tungsten carbide or cobalt alone (Lasfargues et al. 1995). Potential mechanisms for this phenomenon are discussed in Section 3.5.2.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to tungsten or tungsten compounds than will most persons exposed to the same level of tungsten or tungsten compounds in the environment.

Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of tungsten or compromised function of organs affected by tungsten or tungsten compounds. Populations who are at greater risk due to their unusually high exposure to tungsten or tungsten compounds are discussed in Section 6.7, Populations With Potentially High Exposures.

Individuals with compromised respiratory function may exhibit increased sensitivity to airborne tungsten due to irritant properties of tungsten particles that may be deposited in the lungs. Individuals with compromised renal function may also experience particular sensitivity to tungsten since the chemical is excreted rapidly in the urine following absorption. Russian studies indicate that developing fetuses may be particularly sensitive to tungsten. However, these studies are limited in reporting of study details, which renders them of questionable value for purposes of risk assessment.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to tungsten or tungsten compounds. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to tungsten or tungsten compounds. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

No texts were located regarding treatment following exposures to tungsten or tungsten compounds.

3.11.1 Reducing Peak Absorption Following Exposure

No data were located regarding reduction of peak absorption of tungsten following exposure. Cathartics such as magnesium sulfate, as well as gastric lavage, might shorten the transit time of ingested tungsten in the gastrointestinal tract. Oral administration of activated charcoal shortly following oral exposure to tungsten might be effective in reducing peak absorption.

3.11.2 Reducing Body Burden

No data were located regarding reducing the body burden of tungsten.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

No data were located regarding reduction of the toxic effects of tungsten through interfering with mechanisms of action.

3.12 ADEQUACY OF THE DATABASE

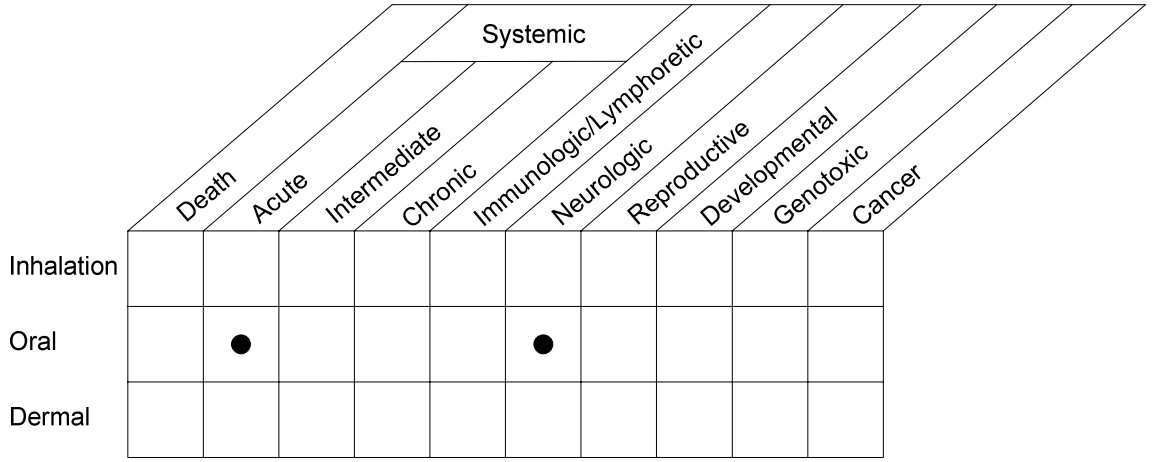
Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of tungsten and tungsten compounds is available. Where adequate 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 tungsten and tungsten compounds.

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 the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

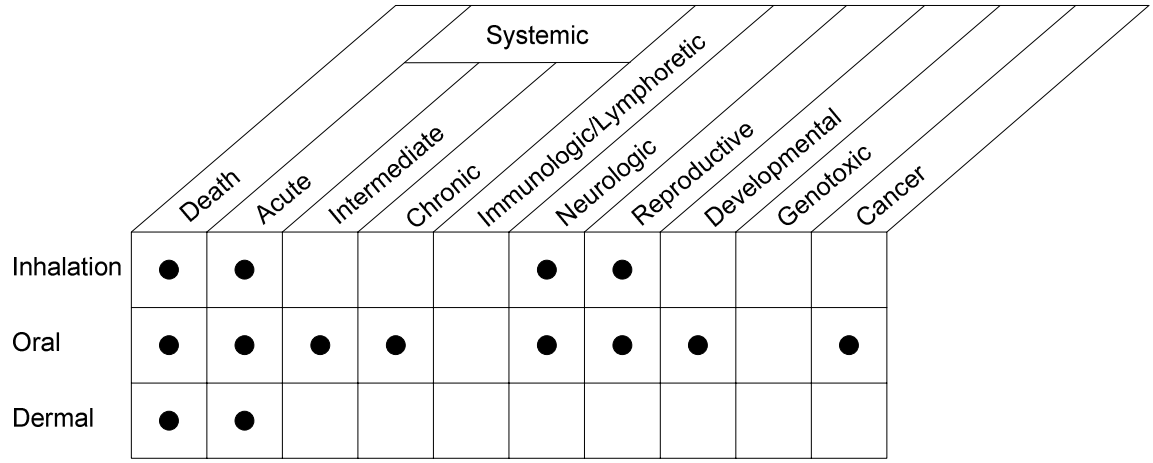
3.12.1 Existing Information on Health Effects of Tungsten and Tungsten Compounds

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to tungsten and tungsten compounds are summarized in Figure 3-6. The purpose of this figure is to illustrate the existing information concerning the health effects of tungsten and tungsten compounds. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct

Figure 3-6. Existing Information on Health Effects of Tungsten and Tungsten Compounds



Human



Animal

● Existing Studies

comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Available data regarding health effects in humans exposed to tungsten predominantly involves occupational exposure to dusts that include particles of tungsten and other metals (particularly cobalt) at facilities in which hard metal is produced. It is generally considered that cobalt is the source of adverse health effects such as pulmonary fibrosis and dermatitis in hard metal workers, not tungsten. A single case report was located concerning acute oral exposure to tungsten in a male subject. However, reported symptoms could not be specifically attributed to tungsten.

Relatively few reports were located regarding health effects in animals following acute-, intermediate-, or chronic-duration exposure to tungsten or tungsten compounds. Several early Russian reports were located, mainly originating from a single group of investigators. The reports predominantly assessed acute lethality or reproductive or developmental effects following oral exposure to soluble tungsten compounds. The carcinogenicity and genotoxicity of tungsten and tungsten compounds has not been adequately assessed in humans or animals. However, tungsten has been recently nominated by the National Center for Environmental Health for toxicological characterization including carcinogenicity (NTP 2003).

3.12.2 Identification of Data Needs

Acute-Duration Exposure. No human studies were located regarding health effects associated with acute-duration inhalation exposure to tungsten. Information in animals is restricted to exposure via intratracheal instillation of tungsten compounds. Intratracheal instillation of water-insoluble calcium tungstate crystals resulted in an inflammatory response in mice (Peão et al. 1993). Acute pulmonary edema was reported in rats that had received hard metal (tungsten carbide and cobalt alloy) via intratracheal instillation, but not in rats exposed to tungsten carbide or cobalt alone (Lasfargues et al. (1992). Due to the lack of information concerning adverse effects and targets of toxicity following acute-duration inhalation exposure to tungsten or tungsten compounds, no acute-duration inhalation MRLs were derived. Results of acute-duration inhalation toxicity studies that adequately characterize dose-response characteristics and target organs could serve as a basis to derive acute-duration inhalation MRLs for tungsten and tungsten compounds.

Information regarding health effects in humans following acute-duration oral exposure to tungsten is restricted to a single case report in which a male subject experienced neurological (nausea, seizure, and 24-hour coma) and renal (temporary renal failure, tubular necrosis, and anuria) effects following the accidental consumption of tungsten in a mixture of beer and wine (Marquet et al. 1997). However, the observed effects could not be specifically attributed to tungsten. Reports of tungsten-induced adverse health effects in animals following acute-duration oral exposure to tungsten consist primarily of reports in which lethality was assessed (Karantassis 1924; Kinard and Van de Erve 1941; Nadeenko 1966; Smyth et al. 1969). Guinea pigs exhibited clinical signs that included trembling and abnormal locomotory behavior following single oral administration of sodium tungstate at ultimately lethal doses (≥780 mg/kg) (Karantassis 1924). Due to the lack of information concerning adverse effects and targets of toxicity following acute-duration oral exposure to tungsten or tungsten compounds, no acute-duration inhalation MRLs were derived. Results of acute-duration oral toxicity studies that adequately characterize dose-response characteristics and target organs could serve as a basis to derive acute-duration oral MRLs for tungsten and tungsten compounds.

Information concerning dermal effects in humans exposed to tungsten is restricted to a report of dermatitis in employees of the hard metal industry, but results of patch testing implicated cobalt, not tungsten, as the causative agent (Schwartz et al. 1945; Skog 1963). Relatively little information is available concerning adverse effects in animals following acute-duration dermal exposure to tungsten. Contact dermatitis was reported in rabbits following dermal application of a 5% tungsten chloride solution in single doses ≥100 mg/kg; doses ≥200 mg/kg also resulted in death (Dow Chemical Company 1982). Instillation of a 5% tungsten chloride solution into the rabbit eye resulted in initial ocular irritation that resolved within 14 days postinstillation (Dow Chemical Company 1982). Additional animal studies could be designed to assess the sublethal systemic toxicity of tungsten and selected tungsten compounds following acute-duration dermal exposure.

Intermediate-Duration Exposure. No human studies were located regarding health effects associated with intermediate-duration inhalation exposure to tungsten. Rats that were repeatedly exposed to atmospheres containing tungsten carbide at a concentration of 600 mg/m^3 exhibited signs of pulmonary fibrosis and clinical signs that were interpreted as anxiety manifestations (Mezentseva 1967). Decreased sperm motility was noted in rats continuously repeatedly exposed to atmospheres containing sodium tungstate at concentrations ≥0.5 mg/m^3 (Idiatullina 1981). Mixed results were reported in laboratory animals following intratracheal instillation of selected tungsten compounds and examinations that spanned intermediate-duration post instillation periods. Signs of pulmonary fibrosis were reported in rats

observed for up to 8 months following intratracheal instillation of metallic tungsten, tungsten trioxide, or tungsten carbide (Mezentseva 1967). Lung lesions in the absence of apparent pulmonary fibrosis were reported in guinea pigs that had received 3 weekly doses of intratracheally-instilled metallic tungsten or tungsten carbide and carbon dust, followed by up to 12 months of posttreatment examination (Delahant 1955; Schepers 1955a, 1955b). No signs of a fibrotic response were seen in the lungs of mice that had received tungsten carbide via intratracheal instillation (Lardot et al. 1998). Due to the lack of information concerning adverse effects and targets of toxicity following intermediate-duration inhalation exposure to tungsten or tungsten compounds, no intermediate-duration inhalation MRLs were derived. Results of intermediate-duration inhalation toxicity studies that adequately characterize dose-response characteristics and target organs could serve as a basis to derive intermediate-duration inhalation MRLs for tungsten and tungsten compounds.

No human studies were located regarding health effects associated with intermediate-duration oral exposure to tungsten. In rats, early reports have associated repeated oral exposure to tungsten with neurological (Karantassis 1924), reproductive (Nadeenko and Lenchenko 1977; Nadeenko et al. 1977, 1978), and developmental (Nadeenko and Lenchenko 1977; Nadeenko et al. 1977, 1978) effects. Body weight changes, in the absence of other signs of toxicity, were reported in rats following repeated oral exposure to various tungsten compounds (Kinard and Van de Erve 1941, 1943). However, the available animal studies did not include critical dose-response information and other details (including methods used in statistical analysis of data), which precludes their usefulness for the purpose of MRL derivation. Therefore, no intermediate-duration oral MRLs were derived for tungsten. Results of intermediate-duration oral toxicity studies that adequately characterize dose-response characteristics could serve as a basis to derive intermediate-duration inhalation and oral MRLs for tungsten and tungsten compounds.

No human or animal data were located regarding noncancer or cancer end points associated with intermediate-duration dermal exposure to tungsten or tungsten compounds.

Chronic-Duration Exposure and Cancer. Information regarding chronic exposure of humans to tungsten primarily involves respiratory effects such as pulmonary fibrosis, memory and sensory deficits, and increased mortality due to lung cancer in hard metal workers exposed to dusts that include particles of tungsten and other metals (particularly cobalt) (see Bech 1974; Bech et al. 1962; Coates and Watson 1971a, 1971b; Jordan et al. 1990; Kaplun and Mezentseva 1959; Lasfargues et al. 1994; Mezentseva 1967; Miller et al. 1953; Moulin et al. 1998; Vengerskaya and Salikhodzhaev 1962). It is generally considered that cobalt is the source of major toxicity concern, not tungsten (see Davison et al. 1983;

Harding 1950). However, it has been suggested that tungsten oxide fibers may contribute to the development of pulmonary fibrosis in hard metal workers (Sahle 1992). No studies were located regarding chronic-duration inhalation exposure of laboratory animals to tungsten or tungsten compounds. Based on the lack of human and animal data, no chronic-duration inhalation MRLs were derived for tungsten or tungsten compounds. Results of well-designed chronic-duration inhalation studies in animals could serve as a basis to derive intermediate-duration inhalation MRLs for tungsten and tungsten compounds.

No human studies were located regarding noncancer or cancer end points associated with chronic-duration oral exposure to tungsten. Information concerning health effects in animals following chronic-duration oral exposure to tungsten or tungsten compounds is restricted to reports by Schroeder and Mitchener (1975a, 1975b) in which tungsten-treated (5 ppm of tungsten as sodium tungstate in the drinking water for a lifetime) and control rats and mice exhibited similar growth patterns and incidences of gross tumors. However, these studies were limited to assessment of growth, gross tumor incidence, and longevity. Limited study design, including lack of both dose-response data and comprehensive histopathologic examinations preclude their usefulness for MRL derivation. Results of well-designed chronic-duration oral studies in animals could serve as a basis to derive intermediate-duration oral MRLs for tungsten and tungsten compounds.

Recent findings of elevated tungsten body burdens in residents of Churchill County, Nevada (CDC 2003b), and the discovery that a relatively limited amount of information is available concerning the potential for long-term adverse health effects following exposure to tungsten, have resulted in the nomination of tungsten by the National Center for Environmental Health (NCEH) for toxicological characterization, which includes carcinogenicity (NTP 2003).

No human or animal data were located regarding noncancer or cancer end points associated with chronic-duration dermal exposure to tungsten or tungsten compounds.

Genotoxicity. No information was located regarding tungsten-induced genotoxicity following inhalation, oral, or dermal exposure to tungsten or tungsten compounds in humans or laboratory animals. Sodium tungstate was found to induce mutagenic activity in a bacterial bioluminescence test (Ulitzur and Barak 1988), lambda prophage in *E. coli* (Rossman et al. 1984, 1991), and gene conversion and reverse mutation in *Saccharomyces cerevisiae* (Singh 1983). An unspecified form of tungsten enhanced mutagenic activity in *Salmonella typhimurium* (Miller and Page 1999). Tungstate anion induced forward

mutation in Chinese hamster lung V79 cells *in vitro* (Zelikoff et al. 1986). Sodium tungstate did not increase sister chromatid exchanges in human whole blood cultures or cause chromosome aberrations in human lymphocytes or Syrian hamster embryo cells (Larramendy et al. 1981). Nor did sodium tungstate induce morphological transformation in Syrian hamster cells (DiPaolo and Casto 1979). Additional studies could be designed to further assess the potential for tungsten and tungsten compounds to induce genotoxicity.

Reproductive Toxicity. No information was located regarding reproductive toxicity in humans following inhalation exposure to tungsten or tungsten compounds. Information in animals is restricted to a single account of decreased sperm motility (10–12% lower than controls) in male rats continuously exposed to atmospheres containing sodium tungstate powder for 17 weeks at concentrations of 1.0 and 0.5 mg/m^3, but not at 0.1 mg/m^3 (Idiatullina 1981).

No information was located regarding reproductive toxicity in humans following oral exposure to tungsten or tungsten compounds. Information in animals is restricted to reported embryotoxicity (expressed as increased percentages of pre- and post-implantation losses, relative to controls) following oral administration of an unspecified tungsten compound to adult female rats at a single dose level of 0.005 mg/kg for up to 8 months before and during pregnancy (Nadeenko and Lenchenko 1977; Nadeenko et al. 1977, 1978). However, the data were poorly presented and study details such as the form of tungsten administered, the specific route of administration, whether the losses were assessed on a per litter basis or per treatment group, and the magnitude of the treatment-related losses, were lacking. Additional well-designed animal studies would be useful to adequately assess the reproductive toxicity of orally-administered tungsten and tungsten compounds. Such studies could include standard reproductive toxicity studies as well as conventional intermediate-duration oral toxicity studies that would include an assessment of reproductive organ pathology.

No information was located regarding reproductive toxicity in humans or animals following dermal exposure to tungsten or tungsten compounds. However, inhalation is the most likely significant route of exposure to tungsten or tungsten in workers employed in industries that produce or use tungsten-containing products. Elevated levels of tungsten in groundwater, such as was detected in well water in Churchill County, Nevada (CDC 2003b), indicate the potential for significant oral exposure to tungsten and tungsten compounds as well. It does not appear that additional studies of health effects associated with dermal exposure to tungsten or tungsten compounds are necessary at this time.

Developmental Toxicity. No information was located regarding developmental toxicity in humans or animals following inhalation exposure to tungsten or tungsten compounds. Animal studies could be performed to assess the potential for tungsten-induced developmental effects via the inhalation exposure route.

No information was located regarding developmental toxicity in humans following oral exposure to tungsten or tungsten compounds. Information in animals is restricted to reported delayed fetal skeletal ossification following oral administration of an identified tungsten compound to adult female rats at a single dose level of 0.005 mg/kg for up to 8 months before and during pregnancy (Nadeenko and Lenchenko 1977; Nadeenko et al. 1977, 1978). However, the data were poorly presented and study details, such as the form of tungsten administered, the specific route of administration, and the magnitude of the treatment-related losses, were lacking. Additional well-designed animal studies should be performed to adequately assess both pre- and post-natal potential for tungsten-induced developmental effects via the oral exposure route.

No information was located regarding developmental toxicity in humans or animals following dermal exposure to tungsten or tungsten compounds. However, inhalation is the most likely significant route of exposure to tungsten or tungsten in workers employed in industries that produce or use tungsten-containing products. Elevated levels of tungsten in groundwater, such as was detected in well water in Churchill County, Nevada (CDC 2003b), indicate the potential for significant oral exposure to tungsten and tungsten compounds as well. It does not appear that additional studies of health effects associated with dermal exposure to tungsten or tungsten compounds are necessary at this time.

Immunotoxicity. No information was located concerning tungsten-induced immunotoxicity in humans or animals following inhalation, oral, or dermal exposure to tungsten or tungsten compounds. A single report was located in which a marked inflammatory response characterized by infiltration of leukocytes in the lungs of mice following intracheal instillation of water-insoluble calcium tungstate powder (Peão et al. 1993). The inflammatory response was likely the result of local irritation rather than an adverse immunological effect. Repeated exposure animal studies by the inhalation exposure route could be designed to assess the immunotoxicity potential of tungsten.

Neurotoxicity. No human data were located in which neurological signs could be associated with inhalation, oral, or dermal exposure to tungsten. Signs of memory and sensory deficits have been reported among workers in the hard metal industry who were exposed to atmospheres of hard metal dusts

(Jordan et al. 1990; Kaplun and Mezentseva 1959; Vengerskaya and Salikhodzhaev 1962); however, these effects likely reflect exposure to cobalt, not tungsten. No studies were located regarding neurological effects in animals following inhalation exposure to tungsten or tungsten compounds. Results of available animal studies indicated clinical signs of neurotoxicity following acute oral dosing at levels resulting in death (Karantassis 1924) and learning deficits and brain lesions following repeated oral dosing (Nadeenko 1966) at sublethal doses. However, clinical signs at lethal doses are not a reliable indicator of primary neurotoxicity and the report of Nadeenko (1966) was not designed to adequately assess neurotoxicity end points. Additional well-designed neurotoxicity studies in animals exposed to tungsten or tungsten compounds via inhalation or oral exposure routes might serve to adequately assess the potential for tungsten to induce neurotoxicity.

Epidemiological and Human Dosimetry Studies. Pulmonary fibrosis, memory and sensory deficits, and increased mortality due to lung cancer have been associated with occupational exposure to dusts generated in the hard metal industry (Bech 1974; Bech et al. 1962; Coates and Watson 1971a, 1971b; Jordan et al. 1990; Kaplun and Mezentseva 1959; Lasfargues et al. 1994; Mezentseva 1967; Miller et al. 1953; Moulin et al. 1998; Vengerskaya and Salikhodzhaev 1962). Hard metal is an alloy or encapsulated mixture that is composed of tungsten or tungsten carbide and cobalt (primarily, although the alloys may also contain yttrium, thorium, copper, nickel, iron, or molybdenum). Historically, the respiratory and neurological effects observed in hard metal workers have been attributed to cobalt, not tungsten (see Davison et al. 1983; Harding 1950). However, based on the presence of tungsten oxide fibers in air samples taken at some hard metal facilities (Sahle 1992; Sahle et al. 1994) and demonstrations that tungsten oxide fibers are capable of generating hydroxyl radicals in human lung cells *in vitro* (Leanderson and Sahle 1995), it has been suggested that tungsten oxide fibers may contribute to the development of pulmonary fibrosis in hard metal workers.

The most likely identifiable subpopulations exposed to tungsten are workers in the hard metal industry. Available human and animal data do not appear to clearly identify targets of toxicity for tungsten. Additional epidemiological studies of tungsten should attempt to identify exposure scenarios that may not be confounded by other known toxicants. Such exposure scenarios might provide valuable information regarding potential tungsten-induced toxicity. Studies of dosimetry would be useful in future epidemiological studies.

Biomarkers of Exposure and Effect.

Exposure. Tungsten can be detected in blood (Bowen 1966; Hartung 1991), urine (Paschal et al. 1998), feces , and tissue samples (Bowen 1966; Iyengar et al. 1978). Since a large percentage of absorbed tungsten is rapidly eliminated from the body, detection would be most effective within a few days following short-term exposure or termination of longer-term exposure. Additional information regarding relationships between tungsten body burden and exposure levels could improve the ability to monitor workers' exposure to tungsten.

Effect. Biomarkers of effect for tungsten and tungsten compounds have not been definitively identified. Additional animal studies designed to assess health effects associated with tungsten should elucidate biomarkers of effect.

Absorption, Distribution, Metabolism, and Excretion. Human reports demonstrate that inhaled and ingested tungsten may be absorbed, distributed systemically, and eliminated to a large extent in the urine (Marquet et al. 1997; Nicolaou et al. 1987; Wester 1974). Animal studies support the human data and further demonstrate that distribution is rapid and widespread and that urinary excretion is also rapid (Aamodt 1975; Ballou 1960; Kaye 1968). Tungsten that is deposited in bone (Kaye 1968; Kinard and Aull 1945) may be slowly released to the blood and also eliminated mainly in the urine (Kaye 1968). Insoluble forms of orally-administered tungsten are chiefly eliminated in the feces. Tungsten has been detected in hair and nail samples of hard metal workers (Nicolaou et al. 1987). Tungsten ion in the body is not known to be metabolized as such. Additional quantitative information regarding absorption and distribution of inhaled or ingested tungsten and tungsten compounds could be used to improve existing PBPK models of the biokinetics of tungsten (ICRP 1981, 2001; Leggett 1997). Although the dermal exposure route does not appear to be a major human exposure route for tungsten, animal studies could be designed to quantify the toxicokinetics of tungsten following dermal exposure.

Comparative Toxicokinetics. Relatively little information is available regarding comparative toxicokinetics for tungsten and tungsten compounds. Available information concerning absorption, distribution, and elimination of tungsten in rats and dogs (Aamodt 1975; Ballou 1960: Kaye 1968) do not indicate major species-specific differences in biokinetics, Available toxicokinetic data in humans (Marquet et al. 1997; Nicolaou et al. 1987; Wester 1974), which have qualitatively demonstrated that airborne and ingested tungsten is absorbed and eliminated, do not indicate that the biokinetics of tungsten may differ greatly between humans and laboratory animals. Apparent species-specific differences in the dietary requirement for molybdenum (Higgins et al. 1956b), coupled with similarities in the biokinetics of

molybdenum and tungsten, suggest that significant species-specific differences in the biokinetics of tungsten may exist. Additional animal toxicokinetic studies could be designed to identify species-specific differences that could serve to improve existing biokinetic models and elucidate specific mechanisms of action for tungsten.

Methods for Reducing Toxic Effects. Mechanisms concerning absorption, distribution, and toxic action of tungsten have not been studied to date; studies should be designed to identify such mechanisms. No established methods or treatments for reducing the body burden of tungsten were identified in literature searches. No information was located regarding treatments to repair damage or improve compromised function resulting from exposure to tungsten. Well-designed mechanistic studies might provide valuable information that could aid in elucidating treatments to reduce tungsten body burden or repair tungsten-induced damage.

Children's Susceptibility. Results of studies published in Russian journals suggest that developing fetuses may be particularly sensitive to tungsten (Nadeenko and Lenchenko 1977; Nadeenko et al. 1977, 1978). However the reports are limited in presentation of exposure scenarios and quantitative results, which renders them of questionable value in assessing health risks associated with exposure to tungsten. Tungsten has been observed to cross the placenta of pregnant rats and to be distributed to the fetus (Wide et al. 1986). Measurable amounts of tungsten have been observed in the milk of lactating cows (Mullen et al. 1976). However, no information was located regarding potentially significant age-related differences in the biokinetics of tungsten. No information was located regarding the potential for tungsten to interact with other chemicals in such a way to produce age-related differences in resulting toxicity. Based on the lack of information regarding the toxic effects of tungsten and potential for age-related differences in susceptibility, animal studies should be designed to further assess health effects that may be related to tungsten. Some of these studies could be designed to test for potential age-related differences in susceptibility and biokinetics as well.

Child health data needs relating to exposure are discussed in 6.8.1 Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

No ongoing research has been identified in the Federal Research in Progress database (FEDRIP 2003). However, tungsten has been nominated by the National Center for Environmental Health for toxicological characterization including carcinogenicity (NTP 2003). Rationale for the nomination includes the use of tungsten in industrial materials and insufficient available data to assess human health implications of elevated urinary tungsten levels. The NTP Interagency Committee for Chemical Evaluation and Coordination (ICCEC) has recommended that toxicological studies should focus on a representative soluble tungsten compound.

4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Tungsten is a naturally occurring element found in the earth's surface rocks. Tungsten metal typically does not occur as the free element in nature. Of the more than 20 tungsten-bearing minerals, some of the commonly used commercial ones include feberite (iron tungstate), huebnerite (manganese tungstate), wolframite (iron-manganese tungstate), and scheelite (calcium tungstate). Tungsten appears in Group VIB of the periodic table. Natural tungsten is composed of five stable isotopes: ^{180}W (0.12%), ^{182}W (26.5%), ^{183}W (14.3%), ^{184}W (30.6%), and ^{186}W (28.4%). Twenty-eight radioactive isotopes of tungsten are known; most of these isotopes have short half-lives. Tungsten forms a variety of different compounds, such as tungsten trioxide, tungsten carbide, and ammonium paratungstate (Penrice 1997a). Information regarding the chemical identity of elemental tungsten and tungsten compounds is located in Table 4-1.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Tungsten has several common oxidation states (e.g., W[0], W[2+], W[3+], W[5+], and W[6+]). However, tungsten alone has not been observed as a cation. Tungsten is stable, and therefore its most common valence state is +6. The naturally occurring isotopes of tungsten are 180 (0.135%), 182 (26.4%), 183 (14.4%), 184 (30.6%), and 186 (28.4%). Artificial radioactive isotopes of tungsten are 173–179, 181, 185, and 187–189 (O'Neil et al. 2001). Elemental tungsten metal is stable in dry air at room temperature. Above 400 °C, tungsten is susceptible to oxidation. Tungsten is resistant to many chemicals and is also a good electrical conductor (Penrice 1997a). Information regarding the physical and chemical properties of elemental tungsten is located in Table 4-2.

Tungsten compounds differ widely in stereochemistry and oxidation states. Tungsten forms binary halide compounds for all oxidation states between +2 and +6. Oxyhalide compounds are only known for oxidation states +5 and +6. In general, tungsten halogen compounds are reactive toward water and oxygen in air. These compounds are all solid, colored compounds at room temperature, except the fluorides, and many decompose on heating before melting. Tungsten oxides form a series of well-defined ordered phases to which precise stoichiometric formulas can be assigned. The composition of the

Table 4-1. Chemical Identity of Tungsten and Tungsten Compounds[a]

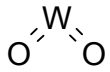
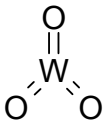
Characteristic	Tungsten	Tungsten oxide	Tungsten trioxide
Synonyms	Wolfram; VA (tungsten)	Tungsten oxide; tungsten dioxide	Tungsten blue; tungsten oxide (WO_3); tungsten trioxide; tungsten(VI) oxide; tungstic acid; tungstic acid anhydride; tungstic anhydride; tungstic oxide; wolframic acid, anhydride
Registered trade name(s)	Tungsten; Wolfram	No data	No data
Chemical formula	W	O_2W	O_3W
Chemical structure	W		
Identification numbers:			
CAS registry	7440-33-7	12036-22-5	1314-35-8
NIOSH RTECS	YO7175000	No data	Y07760000
EPA hazardous waste	No data	No data	No data
OHM/TADS	No data	No data	No data
DOT/UN/NA/ IMCO shipping	No data	No data	No data
HSDB	5036	No data	5800
NCI	No data	No data	77901

Table 4-1. Chemical Identity of Tungsten and Tungsten Compounds[a]

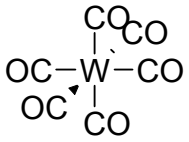
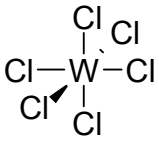
Characteristic	Tungsten carbide	Tungsten carbonyl	Tungsten chloride
Synonyms	Tungsten carbide	Hexacarbonyltungsten; tungsten carbonyl; tungsten hexacarbonyl	Hexachlorotungsten; tungsten hexachloride; wolfram hexachloride
Registered trade name(s)	Tungsten carbide	No data	No data
Chemical formula	CW	C_6O_6W	Cl_6W
Chemical structure	WC		
Identification numbers:			
CAS registry	12070-12-1	14040-11-0	13283-01-7
NIOSH RTECS	No data	Y07705000	Y07710000
EPA hazardous waste	No data	No data	No data
OHM/TADS	No data	No data	No data
DOT/UN/NA/ IMCO shipping	No data	No data	No data
HSDB	2932	No data	No data
NCI	61198	No data	No data

Table 4-1. Chemical Identity of Tungsten and Tungsten Compounds[a]

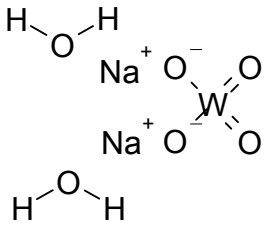
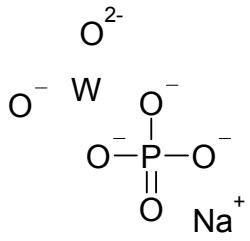
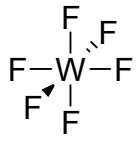
Characteristic	Sodium tungstate, dihydride	Sodium phosphotungstate
Synonyms	Disodium tetraoxatungstate (2-), dihydrate; tetraoxotungstate (2-); disodium tungstate, dihydrate; sodium tungsten oxide, dihydrate; sodium wolframate, dihydrate; tungstic acid, disodium salt, dihydrate	Sodium tungstophosphate; tungstophosphoric acid, sodium salt; sodium-12-tungstophosphate
Registered trade name(s)	No data	No data
Chemical formula	$O_4\ NaW_2 \bullet 2H_2O$ (dihydrate)	ca. $2Na_2OP_2O_5 \bullet 12WO_3 \bullet 18H_2O$
Chemical structure		
Identification numbers:		
CAS registry	10213-10-2 (dihydride); 13472-45-2 (anhydrous)	51312-42-6
NIOSH RTECS	Y07900000; Y07875000	TH5775000
EPA hazardous waste	No data	No data
OHM/TADS	No data	No data
DOT/UN/NA/ IMCO shipping	No data	No data
HSDB	No data; 5057	No data
NCI	No data	No data

Table 4-1. Chemical Identity of Tungsten and Tungsten Compounds[a]

Characteristic	Ammonium paratungstate	Tungstate hexafluoride
Synonyms	APT	Tungsten hexafluoride; tungsten fluoride
Registered trade name(s)	No data	No data
Chemical formula	$H_{24}N_6O_{24}W_7$	F_6W
Chemical structure	$(NH_4)_6W_7O_{24}$	
Identification numbers:		
CAS registry	12028-06-7 (anhydrous); 12208-54-7 (hexahydrate)	7783-82-6
NIOSH RTECS	No data; BS0480000	Y07720000
EPA hazardous waste	No data	No data
OHM/TADS	No data	No data
DOT/UN/NA/IMCO shipping	No data	UN 2196
HSDB	No data	No data
NCI	No data	No data

[a]Sources: Chemfinder 2003; ChemID 2003; HSDB 2003; NIOSH 1990; RTECS 2003

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

Table 4-2. Physical and Chemical Properties of Tungsten and Tungsten Compounds[a]

Property	Tungsten	Tungsten oxide	Tungsten trioxide
Molecular weight	183.85	215.84[b]	231.85
Color	Steel-gray to tin-white	Blue[b]	Canary yellow; dark orange when heated[c]
Physical state	Solid metal	Solid[b]	Solid
Melting point	3,410 °C	1,500–1,700 °C (decomposes)	472 °C
Boiling point	5,900 °C at 760 mm Hg	Not applicable	No data
Density (g/cm^3)	18.7–19.3 °C/4 °C	10.82 (theoretical)	7.2
Odor	No data	No data	No data
Odor threshold:			
Water (mL/g)	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water	No data	Insoluble[b]	Insoluble
Other solvent(s)	Soluble in mixture of nitric acid and hydrofluoric acid	Insoluble in organic solvents[b]	Caustic alkalies; very slightly soluble in acids; slightly soluble in hydrofluoric acid
Partition coefficients:			
K_d (mL/g)	Not applicable	Not applicable	Not applicable
K_{ow}	Not applicable	Not applicable	Not applicable
K_{oc}	Not applicable	Not applicable	Not applicable
Vapor pressure	1.97×10^{-7} mm Hg at 2,327 °C	No data	No data
Henry's law constant	No data	No data	No data
Autoignition temperature	Not applicable	Not applicable	Not applicable
Flashpoint	Not applicable	Not applicable	Not applicable
Flammability limits	Not applicable	Not applicable	Not applicable
Conversion factor	Not applicable	Not applicable	Not applicable
Explosive limits	Not applicable	Not applicable	Not applicable

Table 4-2. Physical and Chemical Properties of Tungsten and Tungsten Compounds[a]

Property	Tungsten carbide	Tungsten carbonyl	Tungsten chloride
Molecular weight	195.85	351.90[b]	396.56[b]
Color	Gray	White[b]	Purple[b]
Physical state	Solid	Solid[b]	Solid[b]
Melting point	2,785 °C	170 °C (decomposes)[b]	275 °C
Boiling point	6,000 °C	Sublimes *in vacuo*[b,d]	346.75 °C
Density (g/cm^3)	15.6	2.65[b]	3.52
Odor	No data	No data	No data
Odor threshold:			
Water (mL/g)	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water	Insoluble	Insoluble[b]	Decomposes[d]
Other solvent(s)	Soluble in nitric acid/hydrogen fluoride; aqua regia	Soluble in organic solvents[b]	Soluble in ethanol, organic solvents[b], lingroin[e]
Partition coefficients:			
K_d (mL/g)	Not applicable	No data	No data
K_{ow}	Not applicable	No data	No data
K_{oc}	Not applicable	No data	No data
Vapor pressure	No data	0.1 mm Hg at 20 °C[c] 1.20 mm Hg at 67 °C[c]	43 mm Hg at 215 °C[e]
Henry's law constant	No data	No data	No data
Autoignition temperature	Not applicable	No data	No data
Flashpoint	Not applicable	No data	No data
Flammability limits	Not applicable	No data	No data
Conversion factor	Not applicable	No data	No data
Explosive limits	Not applicable	No data	No data

Table 4-2. Physical and Chemical Properties of Tungsten and Tungsten Compounds[a]

Property	Sodium tungstate, dihydrate	Sodium phosphotungstate
Molecular weight	329.85[b]	No data
Color	White[b]; colorless[e]	White[c]
Physical state	Solid[b]	Solid[d]
Melting point	Decomposes at 100 °C with loss of water[d] and then melts at 692 °C[f]	No data
Boiling point	Not applicable	No data
Density (g/cm^3)	3.25[b]	No data
Odor	No data	No data
Odor threshold:		
Water (mL/g)	No data	No data
Air	No data	No data
Solubility:		
Water	Very soluble[b]; about 1.1 parts per water (ca. $1x10^6$ mg/L)[c]	Very soluble[e]
Other solvent(s)	Insoluble in alcohol and acids[e]	Very soluble in alcohols[e]
Partition coefficients:		
K_d (mL/g)	No data	No data
K_{ow}	No data	No data
K_{oc}	No data	No data
Vapor pressure	No data	No data
Henry's law constant	No data	No data
Autoignition temperature	Not applicable	No data
Flashpoint	Not applicable	No data
Flammability limits	Not applicable	No data
Conversion factor	Not applicable	No data
Explosive limits	Not applicable	No data

Table 4-2. Physical and Chemical Properties of Tungsten and Tungsten Compounds[a]

Property	Ammonium paratungstate	Tungstate hexafluoride
Molecular weight	1779.16[f]	297.83[b]
Color	White[e]	Colorless[b]; Pale yellow (liquid)[c]
Physical state	Solid[e]	Gas at room temperature[b]
Melting point	No data	2.3 °C[b]
Boiling point	No data	17 °C[b]
Density (g/cm^3)	No data	12.173[b]
Odor	No data	No data
Odor threshold:		
Water	No data	No data
Air	No data	No data
Solubility:		
Water	Soluble[e]	Reacts with water[b]
Other solvent(s)	Insoluble in alcohol[e]	Dissolves in benzene, cyclohexane, or dioxane; soluble in anhydrous hydrogen fluoride[e]
Partition coefficients:		
K_d (mL/g)	No data	No data
K_{ow}	No data	No data
K_{oc}	No data	No data
Vapor pressure (mm Hg)	No data	Gas at room temperature[b]
Henry's law constant	No data	No data
Autoignition temperature	No data	No data
Flashpoint	No data	No data
Flammability limits	No data	No data
Conversion factor	No data	No data
Explosive limits	No data	No data

[a]Information obtained from HSDB 2003, except where noted.
[b]Lide 2000
[c]O'Neil et al. 2001
[d]Penrice 1997b
[e]Lewis 1997
[f]Ashford 1994

tungsten oxide may also vary over a fixed range without change in crystalline structure (Penrice 1997b). A unique characteristic of tungsten is its ability to form condensed complex ions of polytungstates in acid solution (e.g., ammonium paratungstate, $[NH_4]_{10}[H_2W_{12}O_{42}]\cdot 4H_2O$). The tungstate anion ($WO_4^{2-}$) exists in monomeric form only in strongly alkaline solutions. In mildly alkaline solution, the tungstate anions begin to polymerize, and this progresses with decreasing pH (Lassner et al. 1996). Tungstates complexes (WO_4^{2-}) of the alkali metals and magnesium are soluble in water. Tungsten forms hard, refractory, and chemically stable interstitial compounds with nonmetals, particularly carbon, nitrogen, boron, and silicon (Penrice 1997b). Information regarding the physical and chemical properties of tungsten compounds is located in Table 4-2.

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.1 PRODUCTION

Mining of tungsten is almost exclusively by underground methods. Since the tungsten content of typical deposits is only 0.3–1.5% WO_3, all mines have beneficiation facilities that produce a concentrate containing 60–75% WO_3. During the beneficiation process, the ores are crushed and ground in stages with the fine fractions being removed after each stage and the coarse fraction being recirculated. Because tungsten minerals have a high specific gravity, they can be beneficiated by gravity separation, usually by tabling. The ore concentrate may first be pretreated by acid leaching with hydrochloric acid or roasting with soda ash in an autoclave with a solution of aqueous sodium carbonate at ca. 200 °C and a pressure of >11.9 atm. This is followed by digestion to extract the tungsten as sodium tungstate. This compound is subsequently converted to ammonium tungstate by means of a liquid ion-exchange process. The solvent is then evaporated and tungsten is converted to crystalline ammonium paratungstate (APT, $[NH_4]_{10}[H_2W_{12}O_{42}]\cdot 4H_2O$). Tungsten metal powder is obtained from ammonium paratungstate by stepwise reduction with carbon or hydrogen. The reduction is carried out in either tube or rotary furnaces. Tungsten carbide is produced by heating tungsten metal powder and carbon black at high temperatures. The presence of hydrogen or a hydrocarbon gas catalyzes the reaction. Tungsten carbide may also be prepared from oxygen containing tungsten compounds. Tungsten hexachloride is prepared by the direct chlorination of pure tungsten metal in a flow system at 1 atmosphere and 600 °C. Tungsten hexafluoride may be prepared by treating hydrogen fluoride, arsenic trifluoride, or antimony pentafluoride or by direct fluorination of tungsten metal powder. Tungsten hexacarbonyl may be prepared by the aluminum reduction of tungsten hexachloride in anhydrous ether under a pressure of ca. 1 atm of carbon monoxide at 70 °C. Tungsten trioxide is usually prepared from tungstic acid or tungstates (Penrice 1997a, 1997b). Ferrotungsten is produced by carbothermic reduction in an electric arc furnace or by metallothermic reduction with silicon and/or aluminum (Lassner et al. 1996).

No tungsten was reported to have been mined in the United States in 2001. World production of tungsten concentrates was 44,200 metric tons in 2001. The primary world producer of tungsten concentrates is China, which produced 37,000 metric tons in 2001. The U.S. supply of raw tungsten is comprised of imports, tungsten-bearing scrap, releases from industrial stocks, and sales of excess materials from the National Defense Stockpile. Major processors of tungsten materials operating in 2001 included (USGS 2001): Allegheny Technologies Inc.'s Metalworking Products business (Huntsville, Alabama); Buffalo

Tungsten, Inc. (Depew, New York); General Electric Co. (Euclid, Ohio); Kennametal, Inc. (Latrobe, Pennsylvania; Fallon, Nevada); OM Group, Inc. (Midland, Michigan; St. George, Utah); and Osram Sylvania, Inc. (Towanda, Pennsylvania).

Producers of tungsten compounds in the United States in 2002 are as follows (SRI 2002): Tungsten carbide: Alldyne Powder Technologies (Huntsville, Alabama); Dow Chemical U.S.A. (Midland, Michigan; Traverse City, Michigan); Geoliquids, Inc. (Prospect Heights, Illinois); OMG Apex (St. George, Utah); and Osram Sylvania, Inc. (Towanda, Pennsylvania). Tungsten trioxide: Johnson Matthey, Inc. (Ward Hill, Massachusetts); and Osram Sylvania, Inc. (Towanda, Pennsylvania). Tungsten hexafluoride: Air Products and Chemicals (Hometown, Pennsylvania) and Ozark Fluorine Specialties (Tulsa, Oklahoma). Tungsten carbonyl: Strem Chemicals, Inc. (Newburyport, Massachusetts). Tungsten hexachloride: Osram Sylvania, Inc. (Towanda, Pennsylvania).

Since tungsten and tungsten compounds are not covered under Superfund Amendments and Reauthorization Act (SARA), Title III, manufacturers and users are not required to report releases to the EPA's Toxics Release Inventory.

5.2 IMPORT/EXPORT

In 2002 approximately 10,900 metric tons of tungsten concentrates and other forms were imported into the United States amounting to approximately 25% of world production. The largest amounts of tungsten-bearing materials imported for consumption into the United States were from China (e.g., 1,965 metric tons in 2001). Tungsten concentrates and other forms imported for consumption were 13,240, 11,100, 10,180, and 10,830 metric tons for the years 1998, 1999, 2000, and 2001, respectively (USGS 2001, 2003).

In 2002, approximately 3,590 metric tons of tungsten concentrates and other forms were exported from the United States. Exports of tungsten concentrates and other forms were 3,650, 2,886, 2,870, and 5,080 metric tons for the years 1998, 1999, 2000, and 2001, respectively (USGS 2003).

5.3 USE

Tungsten is consumed in the form of tungsten carbide (65%), alloy additives (16%), metallic tungsten (16%), and tungsten chemicals (3%). Tungsten carbide, because of its high hardness at high temperature,

is used as a component of cutting tools, abrasion-resistant surfaces, and forming tools. It is used primarily in the form of cemented carbides, which are used for cutting tools, mining and drilling tools, forming and drawing dies, bearings, valve seats, and several other wear-resistant applications. As an alloy additive, tungsten metal imparts high-temperature strength and wear resistance in steel, nickel, and cobalt-based super-alloys. Metallic tungsten is used as welding electrodes (e.g., thoriated tungsten); in the manufacture of lamp filaments; as an electron emitter; in x-ray and electron tubes; as furnace elements; as heat shields; as vacuum metalizing coils and boats; in glass melting equipment; and as arc-lamp electrodes; in contact points (for vehicle, telegraph, radio, and television equipment), in rocket nozzles and other aerospace applications, and in high-speed rotors (e.g., gyroscopes). It is also used in high-speed impact printers, in glass-to-metal seals, and as a base for silicon semiconductors (O'Neil et al. 2001; Penrice 1997a, 1997b). An increasing use is in military weaponry, in which tungsten alloys are used as an alternate to depleted uranium for armor penetration and tungsten is replacing lead in "green" bullets. Currently, 200 million tungsten bullets are produced annually, using an ounce of tungsten each (>5,500 tons) (ITIA, 2001). Tungsten chemicals, especially the oxides, sulfides, and heterpoly complexes, form stable catalysts for a variety of commercial chemical processes. Tungsten hexachloride is used for preparing tungsten metathesis catalysts and metallic tungsten films. Sodium tungstate is used in the manufacture of heteropolyacid color lakes used in printing inks, plants, waxes, glasses, and textiles and as a fuel-cell electrode material, and in cigarette filters. Other uses of sodium tungstate include the manufacture of tungsten-based catalysts and for fireproofing textiles. Ammonium paratungstate is commercially significant because it is the precursor of high purity tungsten oxides, tungsten, and tungsten carbide powders. Tungsten trioxide is a principal source of tungsten metal and tungsten carbide powders. It is also used as a pigment in oil and water colors, in a wide variety of catalysts, and in the control of air pollution and industrial hygiene (O'Neil et al. 2001; Penrice 1997a, 1997b). Tungsten hexafluoride is used by the electronics industry as a source of tungsten metal that connects the aluminum layers within semiconductor devices (USGS 2001). Ferrotungsten is primarily used as an alloying material in the steel industry (Lassner et al. 1996).

5.4 DISPOSAL

A significant percentage of tungsten is recycled. During the year 2002, the tungsten content of scrap consumed by processors and end-users was estimated at 4,500 metric tons. This represented approximately 35% of apparent U.S. consumption of tungsten in all forms (USGS 2001).

Most tungsten minerals, tungsten compounds, and tungsten-containing materials do not require special disposal and handling requirements. However, some chemical forms may be classified as hazardous materials if the compound is chemically reactive, flammable, or toxic. Care should be taken to read and understand all of the hazards, precautions, and safety procedures for each specific chemical form. In addition, all federal, state, and local laws and regulations should be investigated and subsequently followed with regard to disposal and handling of the specific chemical form of the tungsten compound or material.

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

Tungsten has been identified in at least 6 of the 1,636 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2003). However, the number of sites evaluated for tungsten is not known. The frequency of these sites can be seen in Figure 6-1. Of these sites, all are located within the United States.

Tungsten is naturally released to the atmosphere as windblown dusts. Processes of human origin, such as ore processing, hard-metal fabrication, tungsten carbide production and use, and municipal waste combustion, release tungsten to the atmosphere. Tungsten naturally enters waterways through the weathering of rocks and soils. The sources of anthropogenic releases of tungsten to surface waters include water effluents from tungsten mining and manufacturing processes. Deposition of atmospheric tungsten particulate aerosols from both natural and sources of human origin is also a source of tungsten in surface waters. Some tungsten compounds are naturally present in soil, but the concentration of tungsten in localized soils can be increased by land application of sewage sludge, fertilizers, municipal solid waste ash, and industrial wastes that contain tungsten, or deposition of atmospheric aerosols.

Atmospheric tungsten particulates will eventually settle to the earth's surface by dry deposition or may be removed from the atmosphere by wet deposition (i.e., precipitation). Upon reaching water and soil, tungsten will be in either soluble (e.g., tungstate ion, WO_4^{2-}) or insoluble forms (e.g., tungsten trioxide) in sediment and soil. The mobility of tungsten will depend on environmental conditions such as pH. Under normal environmental conditions, tungsten is expected to have moderate to low mobility. Although chemical reactions may transform one tungsten compound into another, tungsten cannot be degraded by environmental reactions. Data regarding transformation reactions of tungsten in water and soil are limited. No information was available in the literature on the bioavailability of tungsten to plants and animals.

The concentration of tungsten in ambient air is <10 ng/m^3 (Dames et al. 1970; Haddad and Zikobsky 1985; Jagielak and Mamont-Cieśla 1979). Tungsten has not been reported in surface water or groundwater of the United States, except in areas of mineral formations containing tungsten. Tungsten is the 18th most abundant metal, having an estimated concentration in the earth’s surface rocks of

Figure 6-1. Frequency of NPL Sites with Tungsten Contamination

1–1.3 mg/kg (Penrice 1997a). Tungsten concentrations in soils and surface soils are 0.5–83 and 0.68–2.7 mg/kg dry weight, respectively (Senesi et al. 1988). No monitoring data were located for food in the United States. Since tungsten is in soil, the absence of monitoring data for water and food indicates that analytical laboratories may not have been analyzing for this substance. Analyzing such samples using adequately low detection limits could find tungsten at measurable levels. For example, onions collected from 11 Danish sites uncontaminated by human activities other than routine agricultural practices contained tungsten at a mean level of 16.7 µg/kg fresh weight (n=64; range, 6.3–39 µg/kg) (Bibak et al. 1998).

The general population may be exposed to tungsten through inhalation of air and consumption of food. Exposure to tungsten above background levels may occur to the general population living near industries that process or use tungsten or its compounds, and to those living near hazardous sites that contain high concentrations of tungsten. However, the total tungsten intake by the general U.S. population cannot be accurately estimated due to the lack of data regarding tungsten content in food and drinking water. People who work in tungsten manufacturing, fabricating, and reclaiming industries are exposed to higher levels of tungsten and its compounds than the general population.

6.2 RELEASES TO THE ENVIRONMENT

6.2.1 Air

Tungsten naturally occurs in the earth's crust and is released into the atmosphere as a result of natural processes such as entrainment of dust particles and resuspension of soil by wind. Entrainment of soil and dust particles with significant concentrations of tungsten would be most significant in areas with higher soil tungsten concentrations. Human activities, including milling and processing of tungsten and its compounds, burning of coal and municipal solid waste, and land application of fertilizers, release tungsten into the atmosphere.

Tungsten and its compounds may be emitted into the atmosphere during milling and processing operations. In the production of tungsten carbide materials for the hard-metal industry, tungsten oxide fibers were released as a by-product during the reduction stage of the raw material (Sahle et al. 1994). In 1978, Germani et al. (1981) measured an average tungsten concentration of 15±2 ng/m^3 (0.015±0.002 µg/m^3) in particulate emissions from five copper smelters in southeast Arizona. The

concentrations of tungsten in the ore, ore concentrate, and electrostatic precipitator dust from these smelters were 4.0±0.4, 4±1, and 44±8 μg/g, respectively.

Tungsten may be discharged into the atmosphere from the operation of urban municipal waste incineration (MWI) plants. The concentration of tungsten in fly ash from the MWI plants in Barcelona, Spain ranged from 13 to 17 μg/g in two samples (Fernandez et al. 1992). Particle-borne tungsten concentration in stack air emissions of two coal-burning units in a Western U.S. power plant ranged from 2.0 to 23.2 μg/m^3. Atmospheric concentrations of particle-borne tungsten in a power plant plume were 0.019±0.003 μg/m^3, not detected (i.e., 0.0050±0.011 μg/m^3) and not detected at a distance of 0–8, 8–16, and 32–64 km, respectively, from the power plant (Ondov et al. 1989). Air emissions from three different municipal waste deposits in British Columbia, Canada were sampled and analyzed for airborne tungsten compounds (e.g., tungsten carbonyl, $W[CO]_6$). At these locations, tungsten compounds were found at concentrations ranging from 0.005 to 0.01 μg W/m^3 (Feldmann and Cullen 1997).

Tungsten has been identified in outdoor air at one site (i.e., Eastern Michaud Flats Contamination, Idaho) of the six NPL hazardous waste sites where it was detected in some environmental media (HazDat 2003).

6.2.2 Water

Anthropogenic and natural emissions of tungsten to water may result from mining operations and mineral weathering, respectively. Releases to surface water and groundwater typically occur in regions where natural formations of tungsten minerals are prevalent. Tungsten was found in surface water and groundwater in Northern Iceland in areas that had natural formations of tungsten minerals. Concentrations of tungsten in these glacial and thermal waters (2–90 °C) were lower in surface water than in groundwater. Levels of tungsten were 0.03–11.5, 0.015–0.49, 0.005–0.09, 0.005–0.34, and 0.005–0.33 ppb (μg/L) for groundwaters in lowland areas, groundwaters in highland areas, lakes, rivers and streams, and peat soil waters, respectively (Arnórsson and Lindvall 2001). In Japan, the concentration of tungsten was 0.67 mg/L (0.00067 μg/L) in river water (location not specified) polluted with liquid wastes from a tungsten mine (Mamuro et al. 1971).

Tungsten has been identified in groundwater at one site (i.e., Stringfellow, California) of the six NPL hazardous waste sites where it was detected in some environmental media (HazDat 2003).

6.2.3 Soil

Tungsten is naturally present in soils and sediments. Land application of sewage sludge and fertilizers containing higher than background concentrations of tungsten can be an anthropogenic source of tungsten emission to soil. Typical concentrations of tungsten in the lithosphere, parent rocks, and soil amendments such as fertilizers are listed in Table 6-1.

Military installations and areas involved in military combat operations and training may have higher concentrations of tungsten as a result of the use of military hardware containing tungsten. For example, the concentration of tungsten in surface soils samples was measured in areas of atmospheric fallout of particulates from the use of explosives in the Gulf War (1990–1991). In areas nearest to the Saudi Arabian-Kuwait border where the heaviest fall-out occurred, the maximum concentration of tungsten in soil was 126.50 mg/kg (sampling depth of 0–5 cm). In areas 300 km from the border, the concentration of tungsten was 3.25 mg/kg (sampling depth of 0–5 cm) (Sadiq et al. 1992).

Tungsten has been identified in soil at one site (i.e., Anaconda Co. Smelter, Montana) of the six NPL hazardous waste sites where it was detected in some environmental media (HazDat 2003).

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

Tungsten and most tungsten compounds have low vapor pressures at 25 °C and are expected to exist in the particulate phase in air (HSDB 2003; Penrice 1997b). Some exceptions are tungsten carbonyl and tungsten hexafluoride. According to a model of gas/particle partitioning of semivolatile organic compounds in the atmosphere, tungsten carbonyl, which has a vapor pressure of 0.1 mm Hg at 20 °C, is expected to exist in both vapor and particulate phases in the atmosphere (Bidleman 1988; O'Neil et al. 2001). Tungsten hexafluoride is a gas at room temperature (Lide 2000). Vapor- and particulate-phase tungsten compounds may be removed from the air by wet and dry deposition. In Norway, between the years 1993 and 1995, the mean annual wet deposition flux of tungsten ranged from 2 to 10 $\mu g/m^2$ per year (n=13) (Berg and Steinnes 1997). Tungsten-containing soil can be re-suspended into the atmosphere by wind.

Table 6-1. Range and Average Amounts of Tungsten in the Lithosphere, Some Parent Rocks, Some Soil-Added Materials, and Various Fertilizers[a,b]

Material	Concentration (mg/kg)
Lithosphere	(0.1–2.4)
Rock phosphates and phosphorites	(30–270)
Rock carbonates	0.6
Limestones	(0.2–0.8)
Sewage sludges	(1–100)
Manure	(8–2,800)
Calcium cyanamide	0.5
Phosphate fertilizers	100
Ammonium sulfate	(ND–0.03)
Ammonium nitrate	(ND–0.20)
Calcium nitrate	0.23
Urea	(ND–0.11)
Superphosphate	3.84 (1.47–7.04)
Triple superphosphate	3.29 (1.59–4.99)
Potassium sulfate	(ND–0.75)
NP compound	1.28 (ND–3.99)
NPK compound	0.89 (0.02–2.03)

[a]Source: Senesi et al. (1988); detection limit = 0.002 mg/kg
[b]The values presented correspond also to the contribution, in g/ha, of tungsten from 1 mg of fertilizer applied to 1 ha of soil.

ND = not detected; NP = nitrogen and phosphate; NPK = nitrogen, phosphate, and potash

In water, tungsten metal and metal alloys will exist as insoluble solids, while tungsten compounds will exist as ions or insoluble solids (Cotton and Wilkinson 1980). Tungsten compounds are expected to adsorb to suspended soils and sediment in the water column. Tungsten may be present in water as soluble tungstate ions, and also as species with inorganic colloids (Tanizaki et al. 1992). Soluble tungsten compounds (e.g., tungstates) may leach into groundwater. Volatilization from moist soil and water surfaces is not expected to be important for tungsten metal, alloys, and compounds due to their low vapor pressures (HSDB 2003; Penrice 1997b).

Tungsten is carried to rivers, lakes, and oceans by land erosion. The estimated residence time of tungsten in ocean water, before it is removed from the aquatic phase by sedimentation or other removal processes, is approximately 1,000 years (Bowen 1966).

Sorption coefficients for tungsten suggest that it is expected to have moderate to low mobility in soil under normal environmental conditions (Meijer et al. 1998). The sorption coefficient (K_d) for tungsten increases with decreasing pH. The sorption coefficients for tungsten are 100–50,000 at about pH 5; 10–6,000 at about pH 6.5; and 5–90 at pH 8–9 (Meijer et al. 1998). The sorption behavior of tungsten is due to changes in the surface charge of the soil as the contact solution becomes more acidic or alkaline. Tungsten combines with a large number of organic ligands (Lassner et al. 1996). However, no information on stability of tungsten organic matter complexes was located in the literature. Also, no information on the sorption of tungsten in saline environments was located in the literature.

The concentration of tungsten in plants is low (Bowen 1960). No further information was available in the literature on the uptake of tungsten in plants.

No information on the bioavailability of tungsten to animals was available in the literature. Soluble forms of tungsten, such as tungstate ions, will be more bioavailable to fish and animals than insoluble forms. No evidence of the bioaccumulation of tungsten in the food chain of humans was located in the literature.

6.3.2 Transformation and Degradation

Degradation of an element, such as tungsten, is a nuclear process, by definition. Stable elements, such as tungsten, typically undergo such processes only at insignificant rates in the environment. As an element, tungsten cannot degrade chemically. It can change, however, from one chemical form to another,

sometimes reversibly, in numerous chemical reactions that can proceed under a wide range of common environmental conditions.

6.3.2.1 Air

Insoluble particulate-phase tungsten metal, alloys, and compounds are not expected to react in air. Soluble particulate-phase compounds, such as ammonium paratungstate and tungsten hexachloride, may react with moisture in air to form tungstate ions (e.g., WO_4^{2-}). There is no evidence in the literature for interaction of soluble or insoluble particulate-phase tungsten with CO_2 (gas) or other compounds in the atmosphere. No information was found in the literature on photooxidation or photolysis of tungsten compounds in the atmosphere.

6.3.2.2 Water

The reaction of tungsten in water is controlled by chemical speciation by which one species is converted to another. Tungsten exists in several oxidation states, 0, 2+, 3+, 4+, 5+, and 6+ (Bingham et al. 2001). The most stable is 6+ with the lower states being relatively unstable. Tungsten can exist as ions in water with one or more elements such as oxygen. In natural waters, tungsten is primarily in the form of the soluble tungstate ion (i.e., WO_4^{2-}) under alkaline conditions or other tungsten polyanions under acidic conditions (Bowen 1966; Lassner et al. 1996; Tanizaki et al. 1992). Tungsten has a strong tendency to form complexes; this is exemplified by the large series of heteropoly acids formed with oxides of phosphorous (e.g., phosphotungstic acid), arsenic, vanadium, silicon, and others (Bigham et al. 2001). Tungsten combines with a large number of organic ligands (Lassner et al. 1996). However, no information on natural tungsten organic matter complexes was located in the literature.

6.3.2.3 Sediment and Soil

Typical transformation processes for tungsten in soil include precipitation, complexation, and anion exchange. Important factors affecting the transformation of tungsten in soils and sediments include pH, ionic strength (i.e., salinity), concentration and distribution of species, composition of the mineral matrix, organic matter, and temperature. Data suggesting the biotransformation of tungsten or its compounds in soil were not located in the literature.

6.3.2.4 Other Media

No data on the transformation of tungsten in other media were located in available literature.

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

6.4.1 Air

Ambient concentrations of tungsten in air have been measured at levels <10 ng/m^3 (Dames et al. 1970; Haddad and Zikobsky 1985; Jagielak and Mamont-Cieśla 1979). Between 1972 and 1976, mean values of tungsten determined for atmospheric air in Siersza (a small industrial town) and the Warsaw district of Zerań, Poland were 5.8 and 4.5 ng/m^3, respectively, while concentrations in dust were 44 and 19 ppm, respectively, for the same locations (Jagielak and Mamont-Cieśla 1979). The ambient average air concentration of tungsten in the urban air of Montréal, Quebec, Canada was 5.2 ng/m^3 (Haddad and Zikobsky 1985). Dames et al. (1970) measured the concentration of tungsten in urban air at East Chicago, Indiana, an industrial area of northwest Indiana, and Niles, Michigan, which is about 50 miles to the northeast of this industrial area. The concentration of tungsten in suspended particulates from East Chicago, Indiana was 5.8 ng/m^3 while the concentration in samples taken from Niles, Michigan was 0.4 ng/m^3.

Tungsten has been detected at sub-nanogram concentrations at remote locations around the world, possibly the result of natural processes such as entrainment of dust particles and resuspension of soil by wind. The average concentrations of tungsten in particles collected from the Arctic haze of the free troposphere, in the stratosphere, and in the marine boundary over various Arctic regions were as follows (Sheridan and Zoller 1989): North American Arctic, 0.14±0.09 ng/m^3 (n=10); Norwegian Arctic, 0.073±0.031 ng/m^3 (n=9); stratosphere filters, 0.033±0.011 ng/m^3 (n=10); and marine boundary layer filters, 0.095±0.021 ng/m^3 (n=7). The arithmetic mean atmospheric concentration of tungsten at the geographic South Pole was 0.0015±0.0008 ng/m^3 during the Austral summer of 1974–1975 (Maenhaut et al. 1979).

6.4.2 Water

Limited data have been reported on the concentrations of tungsten in surface water and groundwater from the United States. Taylor et al. (1990) reported semi-quantitative concentrations of tungsten in river

waters of the Mississippi River and its tributaries at concentrations ≤0.2 µg/L (i.e., semi-quantitative detection limit of 0.2 µg/L) with 4 of 15 samples showing positive analytical results for tungsten. These results indicate that tungsten may be present in ambient surface waters. However, semi-quantitative results should be interpreted with caution since they may not reflect actual concentration levels. In 1992, water samples were analyzed for three river systems (Truckee, Walker, and Carson, Nevada), which are in regions of natural tungsten mineral formations (Johannesson et al. 2000). The purpose of the study was to assess the interrelationships among metal and other ionic concentrations as the three rivers lost water through evaporation. In the Truckee river system, tungsten varied from a low value of 1.73 nmol/kg (0.319 µg/L) to a high value of 391 nmol/kg (72.1 µg/L). In the Walker and Carson systems, tungsten varied from 0.82 to 22.1 nmol/kg (0.15–4.07 µg/L), and from 8.21 to 1,029 nmol/kg (1.51–189.7 µg/L), respectively. The high concentration of tungsten in these rivers reflects the relative stability of the tungstate ion (WO_4^{2-}) in the alkaline and well-oxygenated waters; contributions from hydrothermal waters; and weathering of rocks/regoliths with high concentrations of tungsten. Samples from these rivers may potentially be potable drinking water sources.

Limited monitoring data were located for urban environments in the United States. Recently, tungsten was found in the municipal water supply of Fallon, Nevada at a concentration of 25 µg/L and in household water from this community at a concentrations ranging from 0 to 217.3 µg/L (CDC 2003b; City of Fallon 2003). No further data were located on the concentrations of tungsten in drinking water from the United States. However, according to EPA sampling and analytical methods, tungsten is not a substance that is typically measured in drinking water.

For non-U.S. locations, tungsten has been detected in surface water from urban areas at higher levels. The levels of tungsten were measured in river water from the Tamagawa and Sagamigawa Rivers located near Tokyo, Japan (Tanizaki et al. 1992a). The range of tungsten concentrations in the dissolved and suspended fractions of these samples were as follows: dissolved fraction (particulates <0.45 µm), 0.0265–0.107 µg/L; dissolved fraction (molecular weight <500), 0.0105–0.0341 µg/L; dissolved fraction (molecular weight=500 to 10^4), 0.0141–0.0701 µg/L; dissolved fraction (molecular weight >10^4), 0–8.7 ng/L; and suspended solids (particulates >0.45 µm), 0–0.104 µg/L. In river water from the Asakawa, Nogawa, and Hisasegawa Rivers and effluent from a sewage treatment plant (all located near Tokyo, Japan), the levels of tungsten were determined to range as follows: dissolved fraction (particulates <0.45 µm), 0.014–0.785 µg/L ; dissolved fraction (molecular weight <500), 0.0206–0.247 µg/L; dissolved fraction (molecular weight=500–10^4), 0.0270–0.537 µg/L; dissolved fraction (molecular weight >10^4), 0–0.0023 µg/L; and suspended solids (particulates >0.45 µm), 0.002–0.060 µg/L (Tanizaki et al. 1992b).

Tungsten was measured in highly solute-rich river systems in a heavily industrialized region of India. Mean concentrations of tungsten in the Mahanadi, Brahmani, and Baitarani Rivers were 0.05 µg/L (range, 0.02–0.9 µg/L), 0.15 µg/L (range, 0.04–0.89 µg/L), and 0.08 µg/L (range, 0.04–0.18 µg/L), respectively (Konhauser et al. 1997).

Locations with natural formations of tungsten have elevated levels of tungsten in surface water and groundwater. The Nahanni River, a spring-fed river system in an area of scheelite/wolframite baring minerals located in Northwest Territories of Canada, was found to contain tungsten at concentrations ranging from <0.1 to 224.5 µg/L (Hall et al. 1988). Tungsten was found in surface water and groundwater in Northern Iceland in areas that had natural formations of tungsten minerals. Concentrations of tungsten in these glacial and thermal waters (2–90 °C) were lower in surface water than in groundwater. Levels of tungsten were 0.03–11.5, 0.015–0.49, 0.005–0.09, 0.005–0.34, and 0.005–0.33 ppb (µg/L) for groundwaters in lowland areas, groundwaters in highland areas, lakes, rivers and streams, and peat soil waters, respectively (Arnórsson and Lindvall 2001).

The concentration of tungsten in seawater is typically about 0.1 µg/L (Bowen 1966).

Tungsten has been detected at low concentrations in rainwater near locations with tungsten emissions. Rainwater analysis performed in the United Kingdom illustrated that ambient tungsten concentrations in rainwater typically are <1 µg/L (Hartung 1991). Kist (1994) determined the levels of tungsten in rainwater sampled 8 km from a hard-metal factory in Russia. The concentrations of tungsten in the solid and soluble phases of rainwater were 0.00014 and 0.00076 µg/L, respectively. The authors suggest that the enrichment of tungsten in the liquid phase may be explained for this area by a high concentration of tungsten as liquid aerosols and vapor-phase compounds rather than particulates.

6.4.3 Sediment and Soil

Tungsten is the 18th most abundant metal, having an estimated concentration in the earth's surface rocks of 1–1.3 mg/kg (Penrice 1997a). Tungsten concentrations in soils and surface soils are 0.5–83 and 0.68–2.7 mg/kg dry weight, respectively (Senesi et al. 1988). Agricultural soils from New Zealand had mean concentrations of tungsten ranging from 1.9 to 21.4 mg/kg (n=2), while mineralized areas had tungsten concentrations ranging from 65 to 125 mg/kg (n=3) (Quin and Brooks 1972a, 1972b). Fu and Tabatabai (1988) measured a mean concentration of 0.89 mg/kg (range, 0–2 mg/kg) for agricultural soils from Iowa (Fu and Tabatabai 1988).

6.4.4 Other Environmental Media

At Cayuga Lake, New York, tungsten was not detected in lake trout (*Salvelinus namaycush*) ranging in age from 1 to 12 years at a detection limit of 0.2 ppb fresh weight (Tong et al. 1974). Sea animals have been reported to contain tungsten in dry tissues at concentrations ranging from $5x10^{-4}$ to $5x10^{-2}$ mg/kg (Bowen 1966).

No monitoring data were located for food in the United States. Onions collected from 11 Danish sites uncontaminated by human activities other than routine agricultural practices contained tungsten at a mean level of 16.7 µg/kg fresh weight (n=64; range, 6.3–39 µg/kg) (Bibak et al. 1998). Blueberries and lingonberries collected from 35 urban and mining area sites in Northern Sweden from September to October 1998 contained tungsten at concentrations of 0.23–3.7 ng/g and 0.22–7.2 ng/g, respectively (Rodushkin et al. 1999). Perez-Jordan et al. (1998) semi-quantitatively determined the concentrations of tungsten in Spanish wines as follows: red-Valencia, 0.25±0.06 ng/mL; red-Utiel-Req, 0.09±0.03 ng/mL; red-Rioja, 0.55±0.05 ng/mL; white-Valencia, 0.25±0.01 ng/mL; white-Utiel-Req, 0.11±0.01 ng/mL; and white-Rioja, 0.6±0.4 ng/mL.

The concentration of tungsten in land plants ranges from 0.0005 to 0.150 mg/kg dry weight (Bowen 1960). Mean concentrations of tungsten in plants were reported as follows: source unknown from New Zealand, 0.27–39.5 mg/kg; tree leaves from New Zealand, 2.2–3.5 mg/kg; and agricultural plants from Iowa, 0.18 mg/kg (Fu and Tabatabai 1988; Quin and Brooks 1972a, 1972b). Quin and Brooks (1972b) determined the tungsten content of some native trees and ferns growing in an area of tungsten mineralization in Westland, New Zealand. The highest value reported was 1,500 mg/kg of ash weight in the leaves of black hard fern (*Blechnum nigrum*). The concentration of tungsten in tree ferns showed a significant correlation with the concentration in the soil; the tungsten content of trees did not. The mean concentration of tungsten in tree bark (oak) sampled from the western part of the Czech Republic was 0.775±0.569 mg/kg (n=389; range, 0.129–4.79 mg/kg) (Böhm et al. 1998). Freitas et al. (1988) measured the concentration of heavy metals in aquatic macrophytes from the Fractal Dam (Tejo River, Portugal) in March 1987. Tungsten was found in whorled-water milfoil (*Myriophyllum verticilatum*), water buttercup (*Ranunculus sp*.), and pondweed (*Potamogetam sp*.) at average levels of 3.1±0.4, 5.6±0.2, and 2.5±0.1 ppm, respectively. Lichen (*Hypogymnia physodes L*.) sampled in Slovenia in 1992 was found to contain tungsten at a mean concentration of 0.17±0.13 µg/g dry weight (n=82, range, 0.04–0.80 µg/g dry weight) (Jeran et al. 1996). Two species of moss (i.e., *Hylocomium splendens* and *Pleurozium schreberi*)

collected around Norway between the years 1993 and 1995 were found to contain tungsten at concentrations of 0.027–0.15 µg/g (n=13) and 0.012–0.093 µg/g (n=13), respectively (Berg and Steinnes 1997). In areas around Norway and Russian Kola peninsula and Tver region, the concentrations of tungsten in moss (*H. splendens*), lichen (*Usnea sp*.), and pine needles (*Pinus sylvestris L*.) were 0.73, <0.2, and 0.34 ppm, respectively (Nazarov et al. 1995).

Tungsten concentrations in the lithosphere, some parent rocks, some soil-added materials, and various fertilizers are illustrated in Table 6–1. Sewage sludge samples from 16 major U.S. cities and Iowa contained tungsten at mean concentrations of 19.4 mg/kg (n=16; range, 0.9–99.6 mg/kg) and 4.3 mg/kg (range, 0.5–62 mg/kg), respectively (Furr et al. 1976; Senesi et al. 1988). The mean concentration of tungsten in sewage sludge samples from 23 U.S. cities was 14.4 ppm dry weight (n=30; range, 0.65–140 ppm dry weight) for samples collected in 1980 (Mumma et al. 1984). Municipal waste ash samples from Japan contained tungsten at median levels as follows: food scrap ash, 0.9 mg/kg (range, 0.24–1.25 mg/kg); animal waste ash, 0.8 mg/kg (range, 0.20–1.56 mg/kg); horticulture waste ash, 1.6 mg/kg (range, 0.86–3.99 mg/kg); sewage sludge ash, 11.8 (range, 5.13–21.5 mg/kg); and incinerator bottom ash, 4.4 mg/kg (range, 2.46–11.4 mg/kg) (Zhang et al. 2002).

Some types of coal may contain tungsten at significant levels. In the United States, tungsten was found in Pocahontas coal at concentrations of 0.5 and 49 ppm dry weight in the organic and sulfide fractions, respectively (Pires et al. 1997). However, it was not detected in any fraction of Davis, Colchester, Herrin, or Pittsburgh coals.

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Although data are limited, the general population may be exposed to trace amounts of tungsten by inhalation of air. Bowen (1966) reported a provisional dietary intake of 49 µg/day for tungsten for a 70-kg man with a diet of 750 g dry weight per day. Since no drinking water data are available for tungsten, an estimated daily intake from drinking water could not be estimated. However, based on limited surface water data for tungsten, the estimated daily intake from drinking water is predicted to be negligible. No information on the concentrations of tungsten in food was located in the available literature.

A National Occupational Exposure Survey conducted by NIOSH during 1981–1983 estimated the number of individuals who were potentially exposed to tungsten and its compounds in the workplace (NIOSH

1983). The total number of individuals occupationally exposed to tungsten was 47,052 (i.e., the sum of three hazard classifications). The number of individuals occupationally exposed to tungsten compounds was as follows (number in parenthesis): sodium tungstate, dihydrate (2,254); sodium tungstate, anhydrous (15,470); sodium phosphotungstate (73); and tungsten carbide (3,395).

Most exposures to tungsten and its compounds in occupational environments occur during production of tungsten metal from the ore, and preparation of tungsten carbide powders. Exposures to cemented tungsten carbide occur in manufacturing and grinding cemented tungsten carbide hard-metal parts. Dusts and mists of tungsten and its compounds or cemented tungsten carbide are produced during crushing, mixing, ball milling, loading and unloading, sintering, cutting, sandblasting, and grinding operations. Because of the high melting points of tungsten compounds, exposures to their vapors are negligible (NIOSH 1977). Table 6-2 lists occupations with potential exposure to tungsten and its compounds.

Tungsten exposure levels for individuals working in the hard-metal industry are illustrated in Table 6-3. In the United States, the breathing zone air concentration of tungsten ranged from 0.2 to 12.8 mg/m^3 for workers involved in the wet grinding of sintered pieces without ventilation (NIOSH 1977). Schwartz et al. (1998) reported that tungsten was found in lung tissues of five individuals occupationally exposed involved in the sandblasting of hard metal tools. The effects of tungsten particulate aerosols on individuals occupationally exposed were studied in a hard metals plant (NIOSH 1977). Of the 178 hard-metal individuals occupationally exposed (52 men and 126 women), 81% were about 30 years old and about 84% of the individuals occupationally exposed had been engaged in hard-metal operations for 3 years. The concentrations of tungsten in the work atmosphere during various operations varied from 0.75 to 6.1 mg/m^3. The ranges of mean tungsten concentrations were 0.8–1.1 mg/L in the blood of 45 individuals occupationally exposed and 0.6–1.1 mg/L in the urine of 40 individuals occupationally exposed, while tungsten was not detectable in the blood of 11 individuals occupationally exposed or in the urine of 7. Individuals occupationally exposed in this factory may have been exposed to both soluble and insoluble tungsten compounds. At a factory in Syracuse, New York, which manufactured hard metal parts from tungsten carbide and cobalt, 1 out of 83 cases of individuals occupationally exposed showed appreciable amounts of tungsten carbide concentrations in the lungs (Auchincloss et al. 1992).

Occupational exposure to tungsten and its compounds have also been observed around the world, especially in hard metal industries. In Milan, Italy, individuals occupationally exposed with an average exposure period of 13 years at job functions such as grinding and cutting hard metal materials, had concentrations of tungsten in tissues as follows: lung, 107 ng/g; blood, 1.35 ng/g; and urine, 12 ng/g

Table 6-2. Occupations with Potential Tungsten Exposure

Alloy makers	Melting, pouring, casting workers
Carbonyl workers	Metal sprayers
Ceramic workers	Ore-refining and foundry workers
Cemented tungsten carbide workers	Paint and pigment makers
Cement makers	Papermakers
Dyemakers	Penpoint makers
Dyers	Petroleum refinery workers
Flameproofers	Photographic developers
High-speed tool steelworkers	Spark-plug makers
Incandescent-lamp makers	Textile dryers
Industrial chemical synthesizers	Tool grinders
Inkmakers	Tungsten and molybdenum miners
Lamp-filament makers	Waterproofing makers
Lubricant makers	Welders

Source: NIOSH 1977

Table 6-3. Worker Exposure to Tungsten in the Hard-Metal Industry

Type of operation	Total dust (mg/m^3)	Tungsten (mg/m^3)	Sample type	Location
Powder processing				
	14.9	7.7	G	Austria
	0.3–9.8	1.8–8.24	B	Switzerland
	1.1–32	0.88–25.6	B	Sweden
	3.1–130.3	2.2–3.5	G	USSR
Tool and operations: casting				
	0.22–7.5	0.52–4.56	B	Switzerland
	15	12	B	Sweden
	0.7–3.0	0.6–2.6	G	Sweden
	5.5–47.7	1.4–2.1	G	USSR
	21.5	17.6	G	Austria
Tool and operations: forming				
	0.5–24.6	0.97–26.7	B	Switzerland
	0.1–7.5	0.08–5.9	B	Sweden
	0.2–0.7	0.17–0.58	G	Sweden
	–	3.3–32.5	G	USSR
	11.1	8.8	B	Austria
Grinding of sintered pieces: wet grinding without exhaust				
	–	0.2–12.8	B	United States

Source: NIOSH (1977) and references within

B = breathing zone; G = general air

(Rizzato et al. 1986). A control group of 17 unexposed individuals in this study had concentrations of tungsten in lung tissue, blood, and urine of 1.5, 0.4, and 0.7 ng/g, respectively. In Germany, 87 individuals occupationally exposed in the hard metal manufacturing industry were assessed for exposure to tungsten (Kraus et al. 2001). The median duration of exposure for these individuals occupationally exposed was approximately 13 years. Ambient monitoring yielded a range of tungsten concentrations from 3.3 to 417.0 μg/m^3 in the production of heavy alloys. The highest tungsten concentrations excreted in urine of individuals occupationally exposed were found in grinders (mean, 94.4 μg/g creatinine; maximum, 169 μg/g creatinine). Thus, despite its low solubility, tungsten carbide was bioavailable. Bioavailability of tungsten and its compounds increases in the order of tungsten metal, tungsten carbide, and tungstate ion (Kraus et al. 2001). At two hard metal manufacturing facilities in Sweden, Sahle et al. (1996) reported total dust personal measurements of 1.2±0.7, 1.6±0.8, and 0.8±0.6 mg/m^3 for ammonium paratungstate (APT), blue oxide ($WO_{2.9}$), and tungsten trioxide (WO_3), respectively. Airborne blue oxide fibers were detected in both static and personal samples when APT was calcined to blue oxide rather than tungsten trioxide.

Occupational exposures have been observed in other industries such as welding shops, smelter/refineries, and shops using tools with cemented tungsten carbide. Brune et al. (1980) determined levels of tungsten in exposed and unexposed individuals from Northern Sweden. Individuals occupationally exposed at a smelter and refinery had levels of tungsten which ranged as follows (n=21): kidney, <0.003–0.018 μg/g wet weight; liver, <0.003–0.014 μg/g wet weight; and lung, <0.003–0.15 μg/g wet weight. The range of concentrations of tungsten in tissues from a control group were as follows (n=8): kidney, <0.003–0.005 μg/g wet weight; liver, <0.003–0.036 μg/g wet weight; and lung, and <0.003–0.011 μg/g wet weight. The concentration of tungsten in the workplace air from welding shops in Montréal, Quebec, Canada averaged 0.67 μg/m^3 (n=13; range, <0.15–1.50 μg/m^3) while the average concentration of tungsten in urban air was 0.0052 μg/m^3 (Haddad and Zikovsky 1985). Lichtenstein et al. (1975) reported the airborne tungsten concentrations in operations involving wet-grinding of tool bits and inserts made of two commercial grades of cemented carbides. The air was sampled with filters in the workers' breathing zones and the filters were analyzed for tungsten. The mean concentration of tungsten was 5.16 mg/m^3 (range, 0.2–12.8 mg/m^3). Of the 25 samples taken, 40% exceeded 5 mg/m^3.

Tungsten may be found in human tissues and body fluids. Serum concentrations of tungsten in healthy human subjects are approximately 1–6 μg/L (Bowen 1966; Hartung 1991). The mean tungsten concentrations in the serum of Swedish 15-year-old adolescents from Uppsala and Trollhättan were 0.14±0.2 μg/L (n=355; range, <0.04–1.8 μg/L) for the period between 1993 and 1994 (Bránáy et al.

2002a), while whole blood concentrations for this same population group were <0.2 µg/L (n=326; range, <0.2–0.94 µg/L).

Tungsten occurs in human urine at low concentrations. As part of the National Health and Nutrition Examination Survey (NHANES III) study from 1988 to 1994, urine specimens were analyzed from a nationally representative sample of some 30,000 persons across the contiguous United States and Alaska (Paschal et al. 1998). The mean concentration of tungsten in urine from this study was 1.92 µg/L (n=496; limit of detection=0.3 ng/mL) for all ages and sexes, while the creatinine adjusted mean concentration was 1.92 µg/g creatinine. Between the years of 1999 and 2000, the geometric mean concentration of tungsten in urine for the U.S. population aged 6 years and older was 0.085 µg/L, while the creatinine adjusted mean concentration was 0.79 µg/L (CDC 2003a). Schramel et al. (1997) reported that the mean concentration of tungsten in urine for 14 unexposed individuals was 0.21±0.09 µg/L.

Tungsten occurs in other body tissues at low concentrations. For example, the concentrations of tungsten in human teeth and mammalian heart tissue were 0.25 and 5 ppb dry weight, respectively (Bowen 1966). For adults, tungsten levels have been determined in human tissues and body fluids: 0.25 ppb in bone; 16 ppb in hair; 2 ppb in heart tissue; <0.7 mg/L in plasma; <0.07 mg/L in serum; 26–160 ppb in skin; 240 ppb in tooth enamel; 2,600 ppb in tooth dentine; and up to 32 µg in urine (Iyengar et al. 1978). Concentrations of tungsten in human teeth, tooth enamel, and tooth dentine vary over a range of 3–6orders of magnitude. These studies, considered together, provide no basis for explanation of these divergent values.

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in 3.7 Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths,

sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

Specific information on the exposure of children to tungsten is limited. As for adults in the general population, small exposures occur from normal ingestion of food and inhaling air. These exposures may be higher in areas near industrial facilities that manufacture, processes, recycle, or use tungsten and its compounds.

At waste sites, tungsten that is found in excess of natural background levels is most likely to be in soil, and presents a special hazard for young children. Hand-to-mouth activity and eating contaminated dirt will result in oral exposure to tungsten. The hazard in this case depends on the form of tungsten present at the waste site. Tungsten in soil at waste sites is in both soluble and insoluble forms; tungsten in insoluble forms would be expected to be less available than more soluble forms.

Tungsten exposure to children from parents' work clothes, skin, hair, tools, or other objects from the workplace is possible if the parent uses tungsten or its compounds at work. However, no cases of home exposure have been reported for tungsten in the literature.

Other home exposures are unlikely since no household products or products used in crafts, hobbies, or cottage industries contain significant amounts of tungsten. One exception is tungsten filaments, which are used in and around the home in light bulbs or other electrical devices.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Several populations are at high risk for exposure to tungsten and its compounds. Individuals with the highest risk include people who are occupationally exposed to tungsten and its compounds from manufacturing, fabricating, or reclaiming industries (see Section 6.5). In particular, occupational exposures have been reported in industries using hard metals, welding shops, smelters/refineries, and shops using tools with cemented tungsten carbide. Occupationally exposed workers who carry tungsten dust on their clothes from the workplace to their home may increase the risk of tungsten exposure to their family members. People living near tungsten-emitting industries may be at a slightly increased risk of tungsten exposure due to contact with tungsten-contaminated dust within the household, as opposed to ambient air levels. Populations living in areas with above-average levels of natural tungsten may be at higher risk to exposure. Recently, tungsten was found in the municipal water supply of Fallon, Nevada at

a concentration of 25 µg/L (ppb) and in household water from this community at a concentration of 3.8 µg/L (CDC 2003b; City of Fallon 2003). This was the first finding of excess community-wide exposure to tungsten. The CDC reported that urine samples of leukemia cases and control subjects from residents in this community had elevated levels of tungsten. The median tungsten level in this study was 0.97 µg/L compared with 0.09 µg/L in the U.S. population. However, no correlation was found in this study between incidents of leukemia and elevated levels of tungsten in urine (CDC 2003b).

6.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, 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 tungsten 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 tungsten.

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 the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. The relevant physical and chemical properties of tungsten and its compounds are available in the literature, but are limited for many tungsten compounds (Ashford 1994; HSDB 2003; Lewis 1997; Lide 2000; O'Neil et al. 2001; Penrice 1997a, 1997b). Additional data on the physical and chemical properties of tungsten compounds would permit estimation of the environmental fate of tungsten and its compounds

Production, Import/Export, Use, Release, and Disposal. Data regarding the past and present production and import/export volumes for tungsten and its compounds are available (SRI 2002; USGS 2001, 2003). Information about the future production of tungsten and its compounds would be useful.

The uses of tungsten and tungsten compounds are well known (ITIA 2001; Lassner et al. 1996; O'Neil et al. 2001; Penrice 1997a, 1997b; USGS 2001). Tungsten and its compounds are widely used in the home and workplace (O'Neil et al. 2001; Penrice 1997a, 1997b). Limited information on the concentrations of tungsten in food was located in the available literature (Bibak et al. 1998; Perez-Jordan et al. 1998; Rodushkin et al. 1999). Additional information would help to determine whether tungsten may be a contaminant in food. Typical releases of the substance in the home, environment, and workplace indicate that water (Arnórsson and Lindvall 2001; HazDat 2003) and air (Feldmann and Cullen 1997; Fernandez et al. 1992; HazDat 2003; Ondov et al. 1989) are likely to be contaminated with tungsten in areas where natural formations occur or where tungsten is used in industry. Most tungsten minerals, tungsten compounds, and tungsten-containing materials do not require special disposal and handling requirements (see Section 5.4). A significant portion of tungsten is routinely recycled (USGS 2001). Since tungsten and tungsten compounds are not covered under Superfund Amendments and Reauthorization Act (SARA), Title III, manufacturers and users are not required to report releases to the EPA's TRI.

Environmental Fate. Information about how tungsten and its compounds partition in the environment is available (Bidleman 1988; HSDB 2003; Lassner et al. 1996; Meijer et al. 1998; O'Neil et al. 2001; Penrice 1997b; Tanizaki et al. 1992), although it is limited in scope. Additional information about the partitioning of tungsten and its compounds would be useful for determining which environmental media tungsten and its compounds are likely to partition to. The mobility of tungsten has been briefly characterized in soil (Meijer et al. 1998). Additional and comprehensive information about the mobility of tungsten and its compounds would be useful in determining the potential of tungsten and its compounds to migrate into groundwater. Tungsten can change from one chemical form to another, sometimes reversibly, in numerous chemical reactions that can proceed under a wide range of common environmental conditions (Bigham et al. 2001; Bowen 1966; Lassner et al. 1996; Tanizaki et al. 1992). However, data on the transformation of tungsten and its compounds are limited. Additional information would help to describe the chemical forms of tungsten and its compounds in different environmental media.

Bioavailability from Environmental Media. The absorption and distribution of tungsten and tungsten compounds as a result of inhalation or dermal exposures, or oral dosing have been discussed. Limited information on the bioavailability (i.e., adsorption from contaminated air, water, or soil) of tungsten and its compounds is available. Updated and more comprehensive data on the bioavailability of tungsten and its compounds from environmental media are needed.

Food Chain Bioaccumulation. Information on the bioconcentration of tungsten and its compounds in plants, aquatic organisms, or animals is not available. Bioconcentration data would be useful in determining the level of storage of tungsten in the organisms as a result of exposure to contaminated media. Information on whether tungsten and its compounds are biomagnified is not available. Biomagnification data would be helpful in determining whether increased levels of tungsten in predators result from consumption of contaminated prey organisms.

Exposure Levels in Environmental Media. Information about concentrations of tungsten and tungsten compounds in air (Dames et al. 1970; Haddad and Zikobsky 1985; Jagielak and Mamont-Cieśla 1979; Maenhaut et al. 1979; Sheridan and Zoller 1989), water (Arnórsson and Lindvall 2001; Bowen 1966; CDC 2003b; City of Fallon 2003; Hall et al. 1988; Hartung 1991; Johannesson et al. 2000; Kist 1994; Konhauser et al. 1997; Tanizaki et al. 1992a, 1992b; Taylor et al. 1990), soil (Fu and Tabatabai 1988; Penrice 1997a; Quin and Brooks 1972a, 1972b; Senesi et al. 1988), and food (Bibak et al. 1998; Perez-Jordan et al. 1998; Rodushkin et al. 1999) are available, but limited. Updated and more comprehensive data on the concentration levels of tungsten in air, water, soil, and food would be useful to provide a more comprehensive characterization of human exposure. Additional data would also be useful in describing historical trends in tungsten concentrations in various environmental media. Reliable monitoring data for the levels of tungsten in contaminated media at hazardous waste sites are needed so that the information obtained on levels of tungsten in the environment can be used in combination with the known body burden of tungsten to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites. Estimates have not been made for human intake of tungsten and its compounds from various environmental media. These data would help to determine the potential for human exposure to tungsten and its compounds.

Exposure Levels in Humans. Tungsten has been detected in the following human tissues and fluids: blood, plasma, and serum (Bowen 1966; Bránáy et al. 2002a; Hartung 1991; Iyengar et al. 1978); urine (CDC 2003a; Iyengar et al. 1978; Paschal et al. 1998; Schramel et al. 1997); teeth (Bowen 1966; Iyengar et al. 1978); heart tissue (Bowen 1966); bone (Iyengar et al. 1978); and hair (Iyengar et al. 1978). However, exposure level data are not current and do not focus on exposed populations (e.g., individuals living near hazardous waste sites). This information would be useful in assessing the need to conduct health studies on these populations.

Exposures of Children. Children may be exposed to tungsten and tungsten compounds in the same manner as adults in the general population (e.g., air, food, and water). Exposure and body burden studies

on children would be useful. No information was available on unique exposure pathways for children (e.g., pica children and dermal). Studies may be needed to determine if unique exposure pathways exist for children. No data were available on the weight-adjusted intake of tungsten. Accordingly, studies would help to determine if children or more or less exposed to tungsten than adults. No childhood-specific means to decrease exposure were identified. Child health data needs relating to susceptibility are discussed in 3.12.2 Identification of Data Needs: Children's Susceptibility.

Exposure Registries. No exposure registries for tungsten were located. This substance is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The substance 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 exposure to this substance. The population of Churchill County (City of Fallon), Nevada is known to have unusually high exposures to tungsten (CDC 2003b; City of Fallon 2003). However, no exposure registry has been established for this population.

6.8.2 Ongoing Studies

No ongoing studies investigating potential for human exposure of tungsten or its compounds were identified in the Federal Research in Progress database (FEDRIP 2003).

7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring tungsten, its metabolites, and other biomarkers of exposure and effect to tungsten. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations 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 groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

7.1 BIOLOGICAL MATERIALS

A variety of analytical methods can be used to determine trace concentrations (sub-ppb to ppb) of tungsten in biological tissues. These include inductively coupled plasma-atomic emission spectroscopy (ICP-AES), inductively coupled plasma-mass spectrometry (ICP-MS), and neutron activation analysis (NAA), as well as other techniques, such as atomic absorption spectroscopy (AAS) and UV/Visible spectroscopy (UV/VIS). Table 7-1 lists analytical methods used for determining tungsten and tungsten compounds in biological fluids and tissues.

ICP-AES and ICP-MS have been used to determine tungsten concentrations in biological samples (Bárány et al. 2002a, 2002b; Marquet et al. 1997; Paschal et al. 1998; Schramel et al. 1997). Samples are typically wet ashed with nitric acid at elevated temperatures and then diluted for analysis. Tungsten is quantified by ICP-AES using the emission line at 207.91 nm and by ICP-MS using isotope masses of ^{182}W and ^{186}W. The instrument detection limits have been determined to be 50 µg/L and 0.02–0.3 µg/L for ICP-AES and ICP-MS, respectively. Huang et al. (2002) recently developed a method using chelation ion chromatography (CIC) coupled with on-line detected by ICP-MS. The advantage of this method is the ability to analyze trace amounts of tungsten (and other metals) in complex matrixes such as biological samples. Using a bis-(2-aminoethylthio) methylate (BAETM) resin column, the limit of detection was reported to be <0.05 ng/mL for this method.

Table 7-1. Analytical Methods for Determining Tungsten in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Human blood	Not specified	ICP-MS	0.2 µg/L	No data	Bárány et al. 2002a, 2002b
Human serum	Not specified	ICP-MS	0.04 µg/L	No data	Bárány et al. 2002a, 2002b
Blood and urine	Dilute (and acidify)	ICP-AES	50 µg/L	No data	Marquet et al. 1997
Human hair and nails	Hydrolysis in nitric acid; dilute	ICP-AES	—	No data	Marquet et al. 1997
Human blood and tissue	Dry	NAA	1 µg/mg	No data	Bowen 1960
Human tissues (e.g., kidney, liver, lung)	Deep freeze (or freeze dry); grind to powder	NAA	No data	No data	Brune et al. 1980
Human urine	Dilute (and acidify)	ICP-MS	0.3 ng/mL	No data	Paschal et al. 1998
Human urine	Dilute (and acidify)	ICP-MS	0.02 µg/L	116.5%	Schramel et al. 1997
Animal tissues (e.g., liver, kidney, lung, spleen, brain, etc.)	Wet digestion using $HNO_3/HClO_4$; evaporate to dryness; dissolve in ionic buffer ($LiNO_3/HNO_3$)	DCP-AES	~0.037 µg/L	No data	Frank and Petersson 1983
Rat and dog plasma	None	ICP-AES	100 ng/mL	89–105%	Poucheret et al. 2000

AES = atomic emission spectroscopy; DCP=DC plasma; $HClO_4$ = perchloric acid; HNO_3 = nitric acid; ICP= inductively coupled plasma; $LiNO_3$= lithium nitrate; MS = mass spectrometry; NAA = neutron activation analysis

NAA techniques provide low detection limits for tungsten (0.005 µg tungsten per gram of sample), but there are few reactors at which NAA facilities and expertise are available (Dams et al. 1970). A common NAA procedure for tungsten determination is to produce the short-lived ^{187}W radionuclide (half-life of 24 hours; gamma-lines of 479.3 and 685.7 keV). Counting can be initiated after an irradiation period of 2–5 hours and a cooling period of 20–30 hours (Dams et al. 1970). Biological samples that have been analyzed for tungsten using the NAA technique include human blood and tissues (e.g., kidney, liver, and lung) (Bowen 1960; Brune et al. 1980). Because facilities at which NAA can be performed are extremely limited, NAA's most useful application is as a reference method against which other less expensive and more common methods can be compared for accuracy.

7.2 ENVIRONMENTAL SAMPLES

Many of the basic analytical methods used for determining tungsten in biological media are also used for determining tungsten levels in environmental samples (e.g., soil, water, and air). ICP-AES, ICP-MS, Flame AAS, UV/VIS spectrophotometry, and NAA are the most common techniques utilized for analysis of tungsten in environmental samples. Table 7-2 lists the methods used for determining tungsten in environmental samples.

The NIOSH-recommended technique (Method 7074) for determining tungsten in air uses Flame AAS. Detection limits for tungsten are 50 µg of soluble tungsten per sample and 125 µg of insoluble tungsten per sample using an absorption line at 255.1 nm (NIOSH 1994).

Inductively coupled plasma techniques have been used to measure tungsten concentrations in water samples. Samples are typically filtered and acidified before analysis. Johannesson et al. (2000) used ICP-MS to measure the levels of total tungsten in river water samples. Detection limits for tungsten were 0.8 nmol/kg (0.15 µg/kg). For spring water, Hall et al. (1988) reported detection limits of 0.06 and 1.2 µg/L for ICP-MS and ICP-AES, respectively. In order analyze waters with high concentrations of dissolved solids (e.g., seawater), Huang et al. (2002) employed CIC coupled with ICP-MS and achieved detection limits of <0.05 ng/mL.

UV/VIS spectroscopy has been used to measure tungsten in environmental samples. Parker and Boltz (1968) used UV/VIS spectroscopy at 262 nm to determine total tungsten levels in water samples as a peroxytungstic acid complex. Quin and Brooks (1972a) measured the concentration of tungsten utilizing

Table 7-2. Analytical Methods for Determining Tungsten in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Digest with HNO_3/HF; evaporate to dryness; add NaOH/$NaSO_4$; dilute	Flame AAS	50 µg soluble W per sample; 125 µg insoluble W per sample	No data	NIOSH 1994 (Method 7074)
Workspace air	Filter air; leach soluble W using DI water; dissolve residual W HNO_3/HF after HCl extraction	Flame AAS	10 µg soluble W/L; 8 mg insoluble W per sample	90.8–103% soluble; 90.8–105% insoluble	Hull and Haartz 1980
Workspace/ urban air	Filter air for particulates	NAA	0.20±0.09 µg/m^3	No data	Haddad and Zikovsky 1985
Water	Dilute tungstate solution; add H_2SO_4 and HOOH; dilute	UV/VIS of peroxy-tungstic acid at 262 nm	No data	No data	Parker and Boltz 1968
Water	Add sodium acetate buffer; add benzoin anti-oxime then extract with MIBK; add 1-ephedrine	Flame AAS	0.1 mg/L	No data	Korrey and Goulden 1975
Water (WO_4^{2-})	Add HCl, chloropromazine HCl, and $(NH_4)_2Fe(SO_4)_2$; mix; add HOOH to initiate reaction	Spectro-photometry (λ=525 nm)	~2 µg/L	No data	Tomiyasu and Yonehara 1996
River water	Filter; acidify with HNO_3	ICP-MS	No data	No data	Konhauser et al. 1997
River water	Filter; acidify with HNO_3	ICP-MS	0.8 nmol/kg (0.15 µg/kg)	No data	Johannesson et al. 2000
River water	Filter; acidify with HNO_3	NAA	No data	No data	Tanizaki et al. 1992a, 1992b
Spring water	Acidify with HCl; add oxime dissolved in EtOH and activated charcoal; filter; ash; dissolve in HCl; dilute	ICP-AES ICP-MS	1.2 µg/L 0.06 µg/L	No data	Hall et al. 1988
Polluted waters	Microwave digestion using HF/HCl/HNO_3; column chromatography using Chelex-100 in Na resin; dilute	ICP-AES	30 mg/L	No data	Ferri et al. 1999
Seawater	Acidify, dilute	CIC-ICP-MS	<0.05 ng/mL	No data	Huang et al. 2002

Table 7-2. Analytical Methods for Determining Tungsten in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Seawater	Acidify; add ammonium pyrrolidine dithiocarbamate; add activated charcoal; stir	NAA	0.05 µg/L	No data	van der Sloot et al. 1977
Soil	Dry; digest in aqua regia/perchloric acid; filter; dilute	ICP-AES	No data	No data	Sadiq et al. 1992
Soil, stream sediment, and rocks	Fuse sample with $KHSO_4$; leach with HCl; mix with $SnCl_2$; add dithiol; dissolve with petroleum spirits	UV/VIS of tungsten-dithiol complex at λ=630 nm	~1 ppm	95–105%	Quin and Brooks 1972a
Fertilizers	Digest in HNO_3, HCl, and/or $HClO_4$ acid(s); dilute	ICP-AES	0.002 mg/kg	No data	Senesi et al. 1988
Onion	Digest and redistill in HNO_3; dilute	ICP-MS	0.0180 µg/kg fresh weight	No data	Bibak et al. 1998
Vegetation	Ash; add $SnCl_2$ solution; add dithiol; dissolve with petroleum spirits	UV/VIS of tungsten-dithiol complex at λ=630 nm	0.01 ppm dry weight	95–105%	Quin and Brooks 1972a
Berries	Microwave digestion; dilute	ICP-AES	0.0001 mg/g dry weight	108%	Rodushkin et al. 1999
Wine	Dilute sample to volume.	ICP-MS	0.01 ng/mL	No data	Pérez-Jordán et al. 1998

λ = wavelength; AAS = atomic absorption spectroscopy; AES = atomic emission spectrometry; CIC=chelation ion chromatography; DI = deionized; EtOH = ethanol; HCl = hydrochloric acid; $HClO_4$ = perchloric acid; HF = hydrofluoric acid; HNO_3 = nitric acid; HOOH = hydrogen peroxide; H_2SO_4 = quinine sulfate; ICP = inductively coupled plasma; $KHSO_4$ = potassium hydrogen sulfate; MIBK = methyl isobutyl ketone; MS = mass spectroscopy; NAA = neutron activation analysis; NaOH = sodium hydroxide; $NaSO_4$ = sodium sulfate; $(NH_4)_2Fe(SO_4)_2$ = ammonium iron(II) sulfate; $SnCl_2$ = tin chloride; UV/VIS = ultraviolet-visible spectroscopy; WO_4^{2-} = tungstate ions

a tungsten-dithiol complex with an absorption wavelength at 630 nm. The detection limit for this technique was approximately 1 ppm in soil and 0.01 ppm dry weight in vegetation.

NAA has been used to determine tungsten levels in environmental samples. Haddad and Zikovsky (1985) reported a detection limit of 0.20±0.09 μg/m^3 tungsten using NAA for determining tungsten in workplace/urban air particulate matter. Tungsten levels in seawater have been determined by NAA after first concentrating tungsten on activated charcoal by adsorption as the ammonium pyrrolidine dithiocarbamate complex (van der Sloot et al. 1977). The detection limit is 0.05 μg tungsten/L after a simple chemical separation.

Tomiyasu and Yonehara (1996) determined the concentration of trace amounts of tungstate ions (WO_4^{2-}) using a catalytic spectrophotometric method. In the presence of iron(II), chloropromazine is oxidized by hydrogen peroxide in a hydrochloric acid solution to form a red free radical, which is further oxidized to form a colorless compound. The reaction can be followed by measuring the increase in absorbance of the red free radical at 525 nm. Tungsten(VI) inhibits the color formation, and the maximum absorbance value decreases with an increase in tungsten(VI) concentration. Tungsten(VI) has been determined by this method in the concentration range of 2–500 μg/L.

7.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, 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 tungsten 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 tungsten..

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 the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

Exposure. Analytical methods with satisfactory sensitivity, precision, and reliability are available to determine the levels of tungsten in human tissues and body fluids (Bárány et al. 2002a, 2002b; Marquet et al. 1997; Paschal et al. 1998; Schramel et al. 1997). Existing analytical methods are sensitive enough to measure background levels in the population and levels at which biological effects occur. For example, detection limits of <0.05 ng/mL have been reported for tungsten in biological samples (Huang et al. 2002). Standard methods of analysis for determining the levels of tungsten in human tissues and body fluids are not available and are needed for inter-laboratory comparability of results. Methods for determining levels of tungsten compounds (e.g., tungstate ions) in human tissues and body fluids are not available. Additional methods for determining tungsten compounds in human tissues and body fluids may be useful for determining exposure from different tungsten species.

Effect. There are no known sensitive and specific biomarkers of effect for tungsten. Therefore, no analytical method recommendations can be made for biomarkers of effect for tungsten at the present time.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Sensitive analytical methods are available to measure the levels of tungsten in environmental media (Hall et al. 1988; Johannesson et al. 2000; Konhauser et al. 1997; NIOSH 1994; Quin and Brooks 1972a; Sadiq et al. 1992), although very limited information is available regarding the accuracy and precision of these methods. Further studies would be useful to ascertain the accuracy and precision of methods used to determine tungsten in environmental media so that the reliability of tungsten levels may be assessed. Most analytical methods are sensitive enough to determine levels of tungsten at which health effects may occur. Some of the available methods can be used to detect tungsten at nanogram levels (Huang et al. 2002). Most of these techniques measure total tungsten and do not distinguish among various tungsten compounds. Although limited, methods are available that determine levels of tungstate ions in environmental media (Tomiyasu and Yonehara 1996). Additional methods would be useful in determining environmental levels of specific tungsten compounds such that human exposure to these compounds may be assessed.

7.3.2 Ongoing Studies

No ongoing studies investigating new methods for detection and speciation of tungsten or tungsten compounds were identified in the Federal Research in Progress database (FEDRIP 2003).

8. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding tungsten in air, water, and other media are summarized in Table 8-1.

No MRLs were derived for inhalation or oral exposure to tungsten or tungsten compounds.

EPA has not classified tungsten or tungsten compounds for carcinogenicity, nor has the EPA derived reference concentrations (RfCs) or reference doses (RfDs) for tungsten or tungsten compounds (IRIS 2003). Levels of tungsten and tungsten compounds are not regulated in water.

Table 8-1. Regulations and Guidelines Applicable to Tungsten

Agency	Description	Information		Reference
INTERNATIONAL				
Guidelines:				
IARC	Carcinogenicity classification	No data		
WHO	Drinking water and air quality guidelines	No data		
NATIONAL				
Regulations and Guidelines:				
a. Air:				
ACGIH	TLV (8-hour TWA)			ACGIH 2003
	Tungsten (as W)			
	Metal and insoluble compounds	5 mg/m^3		
	STEL	10 mg/m^3		
	Soluble compounds	1 mg/m^3		
	STEL	3 mg/m^3		
NIOSH	REL (10-hour TWA)			NIOSH 2003
	Tungsten (also applies to other insoluble tungsten compounds [as W])	5 mg/m^3		
	STEL (15-minute TWA)	10 mg/m^3		
NRC	Occupational values			NRC 2003
	Oral ingestion	ALI (µCi)		10 CFR 20,
	^{176}W	$1.0x10^4$		Appendix B
	^{177}W	$2.0x10^4$		
	^{178}W	$5.0x10^3$		
	^{179}W	$5.0x10^5$		
	^{181}W	$2.0x10^4$		
	^{185}W (LLI wall)	$2.0x10^3$		
	^{185}W	$3.0x10^3$		
	^{187}W	$2.0x10^3$		
	^{188}W (LLI wall)	$4.0x10^2$		
	^{188}W	$5.0x10^2$		
	Occupational values			NRC 2003
	Inhalation[a]	ALI (µCi)	DAC (µCi/mL)	10 CFR 20,
	^{176}W	$5.0x10^4$	$2.0x10^{-5}$	Appendix B
	^{177}W	$9.0x10^4$	$4.0x10^{-5}$	
	^{178}W	$2.0x10^4$	$8.0x10^{-6}$	
	^{179}W	$2.0x10^6$	$7.0x10^{-4}$	
	^{181}W	$3.0x10^4$	$1.0x10^{-5}$	
	^{185}W (LLI wall)	$7.0x10^3$	$3.0x10^{-6}$	
	^{187}W	$9.0x10^3$	$4.0x10^{-6}$	
	^{188}W (LLI wall)	$1.0x10^3$	$5.0x10^{-7}$	
OSHA	PEL (8-hour TWA) for general industry	No data		
	PEL (8-hour TWA) for construction industry			OSHA 2003b
	Tungsten (as W)			29 CFR 1926.55,
	Insoluble compounds	5 mg/m^3		Appendix A
	Soluble compounds	1 mg/m^3		

Table 8-1. Regulations and Guidelines Applicable to Tungsten

Agency	Description	Information		Reference
NATIONAL *(cont.)*				
OSHA	PEL (8-hour TWA) for shipyard industry			OSHA 2003a 29 CFR 1915.1000
	Tungsten			
	Insoluble compounds	5 mg/m^3		
	Soluble compounds	1 mg/m^3		
b. Water	No data			
c. Food	No data			
d. Other				
ACGIH	Carcinogenicity classification	No data		
EPA	Carcinogenicity classification	No data		
	RfD	No data		
	Effluent guidelines and standards; nonferrous metals manufacturing point source category applicable to discharges resulting from the production of tungsten at primary tungsten facilities			EPA 2003a 40 CFR 421.100
	Effluent guidelines and standards; nonferrous metals manufacturing point source category applicable to discharges resulting from the production of tungsten or cobalt at secondary tungsten and cobalt facilities processing tungsten or tungsten carbide scrap raw materials			EPA 2003b 40 CFR 421.310
NRC	Effluent concentrations	Air (µCi/mL)	Water (µCi/mL)	NRC 2003 10 CFR 20, Appendix B
	^{176}W	7.0×10^{-8}	1.0×10^{-4}	
	^{177}W	1.0×10^{-7}	3.0×10^{-4}	
	^{178}W	3.0×10^{-8}	7.0×10^{-5}	
	^{179}W	2.0×10^{-6}	7.0×10^{-3}	
	^{181}W	5.0×10^{-8}	2.0×10^{-4}	
	^{185}W (LLI wall)	9.0×10^{-9}	No data	
	^{185}W	No data	4.0×10^{-5}	
	^{187}W	1.0×10^{-8}	3.0×10^{-5}	
	^{188}W (LLI wall)	2.0×10^{-9}	No data	
	^{188}W	No data	7.0×10^{-6}	

Table 8-1. Regulations and Guidelines Applicable to Tungsten

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
NRC	Release to sewers	Monthly average concentration (µCi/mL)	NRC 2003 10 CFR 20, Appendix B
	^{176}W	$1.0x10^{-3}$	
	^{177}W	$3.0x10^{-3}$	
	^{178}W	$7.0x10^{-4}$	
	^{179}W	$7.0x10^{-2}$	
	^{181}W	$2.0x10^{-3}$	
	^{185}W	$4.0x10^{-4}$	
	^{187}W	$3.0x10^{-4}$	
	^{188}W	$7.0x10^{-5}$	
STATE			
a. Air	No data		
b. Water	No data		
c. Food	No data		
d. Other	No data		

[a]The ALIs and DACs for inhalation are given for an aerosol with an activity median aerodynamic diameter (AMAD) of 1 µm and for class D of radioactive material, which refers to their retention (clearance half-times of <10 days) in the pulmonary region of the lung.

ACGIH = American Conference of Governmental Industrial Hygienists; ALI = annual limits on intakes; CFR = Code of Federal Regulations; DAC = derived air concentrations; EPA = Environmental Protection Agency; IARC = International Agency for Research on Cancer; LLI = lower large intestine; NIOSH = National Institute for Occupational Safety and Health; NRC = Nuclear Regulatory Commission; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfD = reference dose; STEL = short-term exposure limit; TLV = threshold limit values; TWA = time-weighted average; WHO = World Health Organization

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10. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—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.

Anthropogenic—Caused by human activities.

Benchmark Dose (BMD)—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

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.

Biomarkers—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.

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.

Case-Control Study—A type of epidemiological study which examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research but are not actual research studies.

Case Series—Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research but are not actual research studies.

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.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study—A type of epidemiological study of a group or groups which examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs—Substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

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.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

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 occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (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.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

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

Incidence—The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

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.

Immunological Effects—Functional changes in the immune response.

***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 has been reported 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 exposure level 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.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

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

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a minimal risk level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

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

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a 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 (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) which represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed.

Organophosphate or Organophosphorus Compound—A phosphorus containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics—The science of quantitatively predicting the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments which, in general, do not represent real, identifiable anatomic regions of the body whereby the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically-based dose-response model which quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates and, possibly membrane permeabilities. The models also utilize biochemical information such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

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 µg/m^3 for air).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentrations for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

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 no-observed-adverse-effect level (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 the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

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.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic, that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed.

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily Threshold Limit Value - Time Weighted Average (TLV-TWA) may not be exceeded.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

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)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

Time-Weighted Average (TWA)—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose$_{(50)}$ (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.

Toxicokinetic—The study of the absorption, distribution and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) 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 lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of one can be used; however a reduced UF of three may be used on a case-by-case basis, three being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any chemical that is foreign to the biological system.

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that

are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agency wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop E-29, Atlanta, Georgia 30333.

APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal risk levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (3-1, 3-2, and 3-3) and figures (3-1 and 3-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 3-1

(1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

(2) Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 3-1).

(5) Species The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to 1,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

(7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

(8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference The complete reference citation is given in Chapter 9 of the profile.

(11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Figure 3-1

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 → **TABLE 3-1. Levels of Significant Exposure to [Chemical x] - Inhalation**

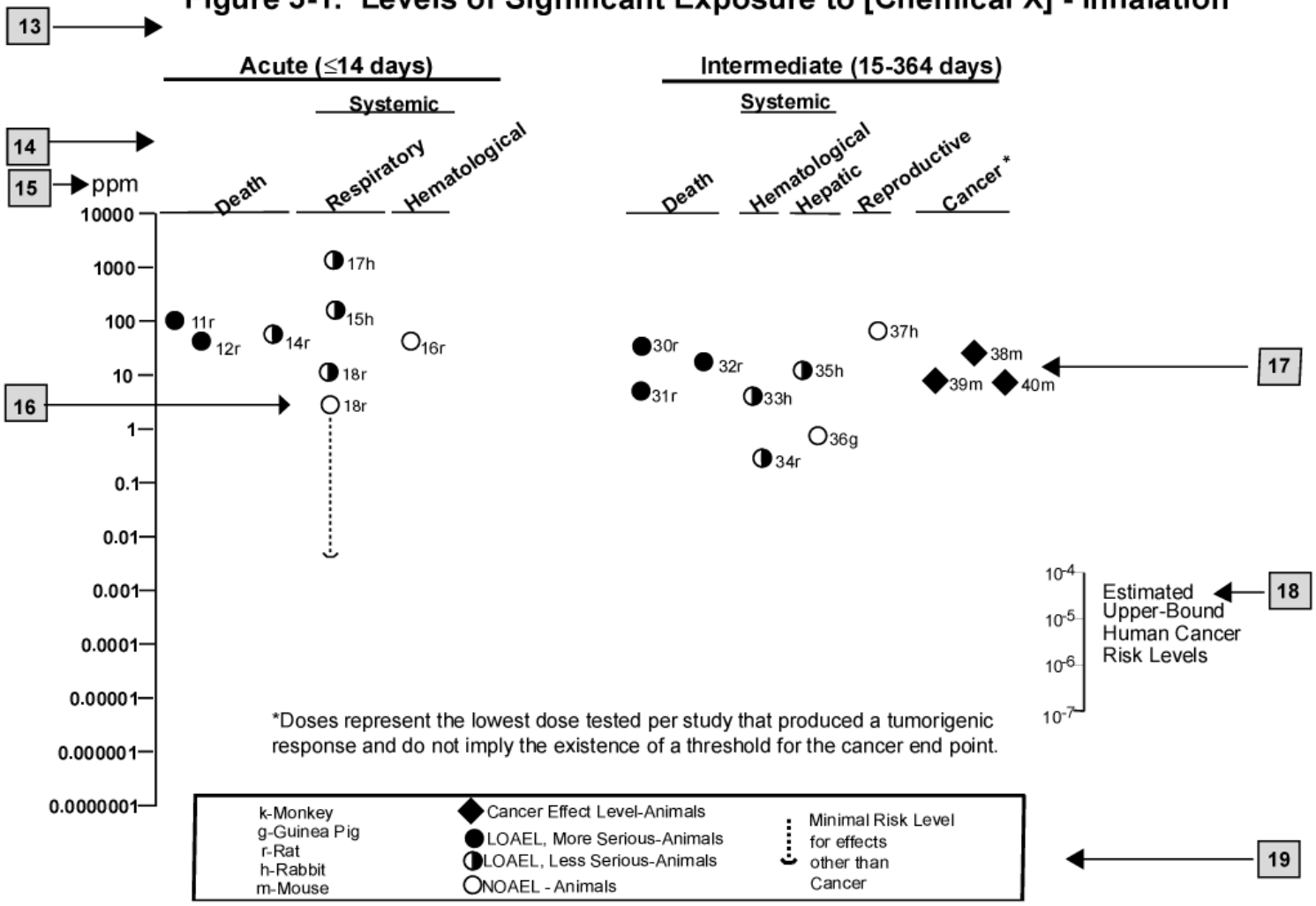
Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
Cancer					11		
					↓		
38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89-104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79-103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 →

[a] The number corresponds to entries in Figure 3-1.

[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5 x 10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACOEM	American College of Occupational and Environmental Medicine
ACGIH	American Conference of Governmental Industrial Hygienists
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AOEC	Association of Occupational and Environmental Clinics
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/International Maritime Dangerous Goods Code

DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	*Federal Register*
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LDH	lactic dehydrogenase
LH	luteinizing hormone
LT_{50}	lethal time, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MFO	mixed function oxidase
mg	milligram

mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes

PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RTECS	Registry of Toxic Effects of Chemical Substances
RQ	reportable quantity
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result