TOXICOLOGICAL PROFILE FOR CADMIUM

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

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DISCLAIMER

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

UPDATE STATEMENT

A Toxicological Profile for cadmium was released in September 1997. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary, but no less than once every three years. 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, 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:

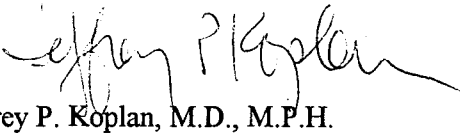
(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(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.



Jeffrey P. Koplan, 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 November 17, 1997 (62 FR 61332). For prior versions of the list of substances, see *Federal Register* notices dated April 29, 1996 (61 FR 18744); 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); and February 28, 1994 (59 FR 9486). 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: Health Effects: Specific health effects of a given hazardous compound are reported by *route of exposure*, by *type of health effect* (death, systemic, immunologic, reproductive), 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 2.6 Children's Susceptibility
Section 5.6 Exposures of Children

Other Sections of Interest:

Section 2.7 Biomarkers of Exposure and Effect
Section 2.10 Methods for Reducing Toxic Effects

ATSDR Information Center

Phone: 1-888-42-ATSDR
or 404-639-6357
Fax: 404-639-6359
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@dgs.dgsys.com • AOEC Clinic Director: http://occ-env-med.mc.duke.edu/oem/aoec.htm.

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: 847-228-6850 • FAX: 847-228-1856.

CONTRIBUTORS

CHEMICAL MANAGER(S)/AUTHORS(S):

Jessilyn Taylor, M.S.
ATSDR, Division of Toxicology, Atlanta, GA

Rob DeWoskin, Ph.D.
Research Triangle Institute, Research Triangle Park, NC

Fanny K. Ennever, Ph.D.
Life Systems Inc., Cleveland, OH

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 cadmium. The panel consisted of the following members:

1. Dr. Joseph P. Gould, Research Scientist, School of Civil & Environmental Engineering, Georgia Institute of Technology, Atlanta, GA;

2. Curtis Klaassen, Professor, Department of Pharmacology and Toxicology, University of Kansas, Kansas City, KS; and

3. R. Craig Schnell, Dean, Graduate Studies and Research, Fargo, ND.

These experts collectively have knowledge of cadmium'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.

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about cadmium 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 a long-term federal cleanup. Cadmium has been found in at least 776 of the 1,467 current or former NPL sites. However, its unknown how many NPL sites have been evaluated for this substance. As more sites are evaluated, the sites with cadmium may increase. This is important because exposure to this substance may harm you and 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 can be 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 cadmium, many factors determine whether you'll be harmed. These factors include the dose (how much), the duration (how long), the chemical or physical form of cadmium present, 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 CADMIUM?

Cadmium is an element that occurs naturally in the earth's crust. Pure cadmium is a soft, silverwhite metal. Cadmium is not usually present in the environment as a pure metal, but as a mineral combined with other elements such as oxygen (cadmium oxide), chlorine (cadmium chloride), or sulfur (cadmium sulfate, cadmium sulfide). Cadmium is most often present in nature as complex oxides, sulfides, and carbonates in zinc, lead, and copper ores. It is rarely present in large quantities as the chlorides and sulfates. These different forms of cadmium compounds are solids

that dissolve in water to varying degrees. The chlorides and sulfates are the forms that most easily dissolve in water. Cadmium may change forms, but the cadmium metal itself does not disappear from the environment. Knowing the particular form of cadmium, however, is very important when determining the risk of potential adverse health effects.

Cadmium compounds are often found in or attached to small particles present in air. Most people can not tell by smell or taste that cadmium is present in air or water, because it does not have any recognizable taste or odor. Soils and rocks contain varying amounts of cadmium, generally in small amounts but sometimes in larger amounts (for example in some fossil fuels or fertilizers).

Most cadmium used in the United States is extracted as a by-product during the production of other metals such as zinc, lead, or copper. Cadmium has many uses in industry and consumer products, mainly in batteries, pigments, metal coatings, plastics, and some metal alloys.

For more information on the properties and uses of cadmium, see Chapters 3 and 4.

1.2 WHAT HAPPENS TO CADMIUM WHEN IT ENTERS THE ENVIRONMENT?

It is estimated that about 25,000 to 30,000 tons of cadmium are released to the environment each year, about half from the weathering of rocks into river water and then to the oceans. Forest fires and volcanoes also release some cadmium to the air. Release of cadmium from human activities is estimated at from 4,000 to 13,000 tons per year, with major contributions from mining activities, and burning of fossil fuels. Cadmium can enter the air from the burning of fossil fuels (e.g., coal fired electrical plants) and from the burning of household waste. Because of regulations, only small amounts currently enter water from the disposal of waste water from households or industries. Fertilizers often contain some cadmium that will enter the soil when fertilizers are applied to crops. Cadmium can also enter the soil or water from spills or leaks at hazardous waste sites if large amounts of dissolved cadmium are present at the site. The form of cadmium at these sites is important since many forms do not easily dissolve in water.

Cadmium that is in or attached to small particles can enter the air and travel a long way before coming down to earth as dust, or in rain or snow. The cadmium metal itself does not break down in the environment, but it can change into different forms. Most forms of cadmium stay for a long time in the same place where they first entered the environment. Some forms of the cadmium that goes into the water will bind to soil, but some will remain in the water. Some forms of cadmium in soil can enter water or be taken up by plants. Fish, plants, and animals can take some forms of cadmium into their bodies from air, water, or food. Cadmium can change forms in the body, but it also stays in the body for a very long time (years).

For more information on how cadmium behaves in the environment, see Chapter 5.

1.3 HOW MIGHT I BE EXPOSED TO CADMIUM?

Food and cigarette smoke are the biggest sources of cadmium exposure for people in the general population. Average cadmium levels in U.S. foods range from 2 to 40 parts of cadmium per billion parts of food (2-40 ppb). Lowest levels are in fruits and beverages, and highest levels are in leafy vegetables and potatoes. Air levels of cadmium in U.S. cities are low, ranging from less than I to 40 nanograms per cubic meter (ng/m^3) (a nanogram is one billionth of a gram). Air levels greater than 40 ng/m^3 may occur in urban areas with high levels of air pollution from the burning of fossil fuels. The level of cadmium in most drinking water supplies is less than 1 ppb, well below the drinking water standard of 50 ppb. Levels in drinking water, however, may vary greatly depending on local conditions. The average level of cadmium in unpolluted soil is about 250 ppb. At hazardous waste sites, cadmium levels have been measured in soil at about 4 parts cadmium per million parts (4 ppm; a part per million is 1,000 times more than a ppb) and in water at 6 ppm. In the United States, the average person eats food with about 30 micrograms (μg) of cadmium in it each day, but only about l-3 μg per day of that cadmium from food is absorbed and enters the body. Cadmium exposure from smoking cigarettes may be a more serious health concern than cadmium in food. Smokers may double their daily intake of cadmium compared with nonsmokers. Each cigarette may contain from 1 to 2 μg of cadmium, and 40-60% of the cadmium in the inhaled smoke can pass through the lungs into the body. This means that smokers

may take in an additional 1-3 μg of cadmium into their body per day from each pack of cigarettes smoked. Smoke from other people's cigarettes probably does not cause nonsmokers to take in much cadmium.

Aside from tobacco smokers, people who live near hazardous waste sites or factories that release cadmium into the air have the potential for exposure to cadmium in air. However, numerous state and federal regulations control the amount of cadmium that can be released to the air from waste sites and incinerators so that properly regulated sites are not hazardous. The general population and people living near hazardous waste sites may be exposed to cadmium in contaminated food, dust, or water from unregulated releases or accidental releases. Numerous regulations and use of pollution controls are enforced to prevent such releases.

Workers can be exposed to cadmium in air from the smelting and refining of metals, or from the air in plants that make cadmium products such as batteries, coatings, or plastics. Workers can also be exposed when soldering or welding metal that contains cadmium. Approximately 512,000 workers in the United States are in environments each year where a cadmium exposure may occur. Regulations that set permissible levels of exposure, however, are enforced to protect workers and to make sure that levels of cadmium in the air are considerably below levels thought to result in harmful effects.

In Chapter 5, you can find more information on how you might be exposed to cadmium.

1.4 HOW CAN CADMIUM ENTER AND LEAVE MY BODY?

Cadmium can enter your body from the food you eat, the water you drink, from particles it may be attached to in the air you breathe, or from breathing in cigarette smoke that contains cadmium. Higher amounts of cadmium can enter your body from the cadmium in air or smoke that you inhale (25 to 60% of the cadmium present) than from cadmium in foods you eat (about 5-10% enters the body). The cadmium not taken into your body through the lungs is breathed out. The cadmium not taken into your body from food or water leaves your body in feces. If you do not

eat foods that contain enough iron or other nutrients, you are likely to take up more cadmium from your food than usual. Virtually no cadmium enters your body through your skin.

Most of the cadmium that enters your body goes to your kidney and liver and can remain there for many years. A small portion of the cadmium that enters your body leaves slowly in urine and feces. Your body can change most cadmium to a form that is not harmful, but too much cadmium can overload the ability of your liver and kidney to change the cadmium to a harmless form, and the harmful form may damage your health.

More information on how cadmium enters and leaves the body is found in Chapter 2.

1.5 HOW CAN CADMIUM AFFECT MY HEALTH?

The potential for cadmium to harm your health depends upon the form of cadmium present, the amount taken into your body, and whether the cadmium is eaten or breathed. There are no known good effects from taking in cadmium. Breathing air with very high levels of cadmium can severely damage the lungs and may cause death. Breathing air with lower levels of cadmium over long periods of time (for years) results in a build-up of cadmium in the kidney, and if sufficiently high, may result in kidney disease. Other effects that may occur after breathing cadmium for a long time are lung damage and fragile bones.

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.

We do not have many good studies on the health effects of cadmium in people. Exposures to cadmium throughout most of the world are currently regulated so there are relatively few people receiving high levels, and the effects from long-term low-level exposure to cadmium are hard to determine with the many other factors that can come into play. A number of studies on workers exposed to cadmium in the air have not resulted in convincing evidence that cadmium can cause lung cancer in humans. In animals studies, mice or hamsters that breathed in cadmium did not get lung cancer, but rats that breathed in cadmium did develop lung cancer. There is no good information on people to suggest that breathing cadmium can affect your ability to have children. Female rats and mice, however, that breathed high levels of cadmium had fewer litters, and their babies may have had more birth defects than usual. Breathing cadmium has also been shown to cause liver damage and changes in the immune system in rats and mice. There is no reliable information on people to indicate that breathing cadmium harms peoples' liver, heart, nervous system, or immune system.

Eating food or drinking water with very high cadmium levels severely irritates the stomach, leading to vomiting and diarrhea, and sometimes death. Eating lower levels of cadmium over a long period of time can lead to a build-up of cadmium in the kidneys. If the levels reach a high enough level, the cadmium in the kidney will cause kidney damage, and also causes bones to become fragile and break easily. We do not have good direct information from people who have been exposed to cadmium to know if eating cadmium at levels, below which other toxic effects are not seen, might effect your ability to have children. Animals eating or drinking cadmium sometimes get high blood pressure, iron-poor blood, liver disease, and nerve or brain damage. We have no good information on people to indicate that the levels that people would need to eat or drink cadmium to result in these diseases, or if they would occur at all. Studies of humans or animals that eat or drink cadmium have not found increases in cancer, although additional research is needed to be more certain that eating or drinking cadmium definitely does or does not cause cancer. Skin contact with cadmium is not known to affect the health of people or animals

because virtually no cadmium can enter the body through the skin under normal circumstances (i.e., without exposure to very high concentrations for long times or exposure to skin that was not damaged).

As a conservative approach, and based on the limited human data and the studies in rats, the United States Department of Health and Human Services (DHHS) has determined that cadmium and cadmium compounds may reasonably be anticipated to be carcinogens. The International Agency for Research on Cancer (IARC) has determined that cadmium is carcinogenic to humans. The EPA has determined that cadmium is a probable human carcinogen by inhalation.
More information on how cadmium can affect your health is found in Chapter 2.

1.6 HOW CAN CADMIUM AFFECT CHILDREN?

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on children resulting from exposures of the parents are also considered.

The health effects seen in children from exposure to toxic levels of cadmium are expected to be similar to the effects seen in adults (kidney, lung, and intestinal damage depending on, the route of exposure). These effects are most easily seen in short-term high-level exposures. Harmful effects on child development or behavior have not generally been seen in populations exposed to cadmium, but more research is needed. It is also difficult to determine the cause of harmful effects on child behavior or development from exposures to low levels over long periods of time, which are the most likely exposures for children as well adults in the general population.
We do not know whether cadmium can cause birth defects in people. Studies in animals exposed to high enough levels of cadmium during pregnancy have resulted in harmful effects in the young. The nervous system appears to be the most sensitive target. Young animals exposed to cadmium before birth have shown effects on behavior and learning. There is also some information from

animal studies that high enough exposures to cadmium before birth can reduce body weights and affect the skeleton in the developing young. Similar effects, however, have not been observed in humans. Humans may respond differently or the exposure levels in humans may be considerably below the levels that produced these adverse effects in animals. More research on human health effects is needed to answer these questions.

Most cadmium taken into the stomach and intestines passes through without being absorbed. At high enough levels, however, damage to the stomach and intestines can occur. A few studies in animals indicate that younger animals absorb more cadmium than adults. Animal studies also indicate that the young are more susceptible than adults to a loss of bone and decreased bone strength from exposure to cadmium. Animal studies also indicate that more cadmium is absorbed into the body from the diet if the diet is low in calcium, protein, or iron, or if the diet is high in fat (because fat slows down the passage of food in the gut and allows more time for absorption). Children who do not get enough iron, calcium, or protein may also absorb more cadmium.

Women with low levels of calcium or iron, due to multiple pregnancies and/or dietary deficiencies, may also absorb more cadmium when exposed to cadmium in food or water. Cadmium does not readily go from a pregnant woman’s body into the developing child, but some can cross the placenta. Cadmium levels in human milk can also be from 5 to 10% of the levels found in the mother’s blood.

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

If your doctor finds that you have been exposed to significant amounts of cadmium, ask your doctor if children may also be exposed. When necessary, your doctor may need to ask your state public health department to investigate.

You can reduce the risk of your family being exposed to cadmium by identifying potential sources of cadmium exposure (in or around your home, at work, or where your children play), and by taking measures to prevent your family members from being exposed. A balanced diet that

includes enough calcium, iron, protein, and zinc will also help reduce the amount of cadmium that may be absorbed into the body from food or drink.

Take an inventory of items in and around your home that might contain cadmium. Examples include fungicides (cadmium chloride), batteries (nickel-cadmium batteries also called Ni-Cad batteries), and hobbies that use materials that contain cadmium (electroplating or welding of metals, some fabric dyes, ceramic and glass glazes). Generally, the label of ingredients for a product will list cadmium or a cadmium compound as an active ingredient, or you can contact the manufacturer and ask whether the item contains cadmium. If you think that a fertilizer might contain cadmium, ask the supplier or the manufacturer. The cadmium in these items would have to get into your body before it could do any harm. This could happen if, for example, a fungicide containing cadmium was accidentally or intentionally swallowed, or if Ni-Cad batteries were being burned in a waste incinerator and a family member was breathing in the smoke, or if you were welding metal alloys that contain cadmium or using a cadmium glaze on a piece of pottery and were breathing in fumes that contained cadmium. You can prevent these exposures by making sure that you and your family members do not accidentally swallow substances that contain cadmium or breathe in air contaminated with cadmium. All cadmium-containing fungicides or dyes should be properly stored, safely out of the reach of children. If you or your family members have a hobby where metals or materials that contain cadmium are being heated or welded, you should seek advice on proper ventilation of your workspace and the proper use of a safety respirator.

Nickel-cadmium batteries are not harmful when properly used, but can release cadmium fumes if burned in an incinerator or waste fire. Breathing in these fumes may be harmful to your health. Small children also may mistake Ni-Cad batteries for toys and may accidentally swallow them. If the battery case is damaged, then some cadmium could escape and come in contact with the stomach or intestines. Keep Ni-Cad batteries out of the reach of small children, and teach your older children that the contents in Ni-Cad batteries can be harmful to their health if swallowed or burned. Teach your family how to properly dispose of the batteries. Information on where to

dispose of Ni-Cad batteries is available from your city or county waste disposal office or the office for a waste disposal service.

If you are using fungicides or fertilizers that contain cadmium on your lawn or garden, read the instructions to learn the safe way to use these materials. One possible route of exposure from fungicides or fertilizers would be from breathing in small particles of cadmium-containing dusts. Protective safety gear including dust masks are available at hardware and building supply stores.

If you have a water well and are concerned that your water may contain cadmium, you can have your water tested. Water filters that remove cadmium, as well as lead and other metals, from drinking water are also available at your local stores. You should ask for advice from your public health officials or from knowledgeable suppliers of water filters on the proper filter or filters to use for your water system.

It is sometimes possible to carry cadmium-containing dust from work on your clothing, skin, hair, tools, or other objects removed from the workplace. This is particularly true when working in buildings where there is smelting or refining of cadmium-containing metal ores, soldering or welding of metals that contain cadmium, or where cadmium batteries, coatings, or plastics are made. You may contaminate your car, home, or other locations outside work where children might be exposed to cadmium.

Your occupational health and safety officer at work can and should tell you whether chemicals you work with are dangerous and likely to be carried home on your clothes, body, or tools and whether you should be showering and changing clothes before you leave work, storing your street clothes in a separate area of the workplace, or laundering your work clothes at home separately from other clothes. If cadmium is being used in your workplace, there should be a material safety data sheet (MSDS) available at your place of work, as required by the Occupational Safety and Health Administration (OSHA). The MSDS information will include the chemical name(s) of any hazardous cadmium ingredients, fire and explosion data, potential health effects, how you get the chemical(s) in your body, how to properly handle the materials, and what to do in an emergency.

Your employer is legally responsible for providing a safe workplace and should freely answer your questions about hazardous chemicals. Your OSHA-approved state occupational safety and health program or OSHA can answer any further questions, and help your employer identify and correct problems with hazardous substances. Your OSHA-approved state occupational health program or OSHA will also listen to formal complaints you would like to make about workplace health hazards and will inspect your workplace, if necessary. Employees have a right to seek safety and health on the job without fear of punishment.

Potential sources of exposure to cadmium away from home include exposures at hazardous waste sites or from air near waste incinerators. Young children should not play near or in hazardous wastes sites, and regulations that prevent this activity are generally enforced. Proper enforcement of regulations also prevents releases of cadmium to the air from waste incinerators or to water from hazardous waste sites. If you or your family live near a hazardous waste site and you have reason to believe that regulations are not being enforced and that you or your children are being exposed to cadmium, contact your local health official and report your concern.

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

You can be tested for exposure to cadmium in several ways. The amount of cadmium in your blood, urine, hair, or nails can be measured by some medical laboratories. The amount of cadmium in your blood shows your recent exposure to cadmium. The amount of cadmium in your urine shows both your recent and your past exposure. Cadmium levels in hair or nails are not as useful as an indication of when or how much cadmium you may have taken in, partly because cadmium from outside of your body may attach to the hair or nails. Tests are also available to measure the amount of cadmium inside your liver and kidneys. The results of these tests can help a doctor evaluate the risk of liver or kidney disease. However, these tests are too costly and inconvenient for routine use. Your urine can be tested to see if your kidneys are damaged. If you do have kidney damage, the urine tests do not prove that cadmium caused the damage.

More information on how cadmium can be measured in exposed humans is presented in Chapters 2 and 6.

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 cadmium include the following:

The government has taken steps to protect humans from excessive cadmium exposure. The EPA allows only up to 5 parts of cadmium per billion parts of water (5 ppb) in drinking water. The EPA also limits how much cadmium can be put into lakes, rivers, dumps, and cropland, and does not allow cadmium in pesticides. The FDA limits the amount of cadmium in food colors to 15 parts per million (ppm).

OSHA now limits the amount of cadmium in workplace air to 5 micrograms per cubic meter ($\mu g/m^3$).

More information on governmental rules regarding cadmium can be found in Chapter 7.

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

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

* Information line and technical assistance

Phone: l-800-447-1544
Fax: (404) 639-6359

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.

* To order toxicological profiles, contact

National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161
Phone: (800) 553-6847 or (703) 487-4650

2. HEALTH EFFECTS

2.1 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 of the toxicology of cadmium. 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:

The form of cadmium and the route of exposure can greatly affect the absorption and distribution of cadmium to various target sites, and therefore, the concentration at the target site and the severity of the observed effect. The mechanism of action, however, involves the cadmium cation's effect on the target site, and the cation is the same regardless of the anionic species. For inhaled cadmium compounds, the size of the cadmium particle (i.e., fume or aerosol) can also affect the absorption and distribution. The form of cadmium that is of most interest for health effects from inhalation exposure is cadmium oxide because that is the main form of airborne cadmium. For oral exposures, cadmium chloride is most often tested in animal studies because of its high water solubility and the resulting high concentrations of cadmium delivered to target sites. Studies on cadmium bound to metallothionein (MT) are also of interest because CdMT complexes may have different toxic profiles and are found in relatively high levels in organ meats (e.g., liver and kidney). Cadmium oxide and cadmium carbonate, which are relatively insoluble in water (but may dissolve at gastric pH), appear to be similar in absorption and toxicity to soluble cadmium. There are fewer studies available on other forms of cadmium including insoluble forms in water such as cadmium sulfide (a yellow pigment) and cadmium selenium sulfide (a red pigment), and a soluble form, cadmium sulfate, which is less soluble in a closed air system where there is a limited amount of dissolved carbon dioxide. Chapter 3 lists the chemical and physical properties of several cadmium compounds.

2.2 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-observedadverse-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 (LOAEL) 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.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of cadmium are indicated in Tables 2-1 and 2-2, and Figures 2-I and 2-2. Because cancer effects could occur at lower exposure levels, Figure 2-l also shows a range for the upper bound of estimated excess risks, ranging from

a risk of 1 in 10,000 to 1 in 10,000,000 ($l0^{-4}$ to $l0^{-7}$), as developed by EPA. Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for cadmium. 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.

2.2.1 Inhalation Exposure

The information in this section on health effects of inhalation exposure to cadmium in humans is derived from studies of workers exposed to cadmium fume or dusts in industries such as smelting, battery manufacturing, soldering, and pigment production. Adverse effects of human exposure to cadmium were first established among workers in a cadmium battery factory (Friberg 1950). Workers are exposed occupationally to cadmium primarily by inhalation of fumes or dust. Some gastrointestinal tract exposure may also occur when dust is removed from the lungs by mucociliary clearance and subsequently swallowed, or by ingestion of dust on hands, cigarettes, or food (Adamsson et al. 1979). In experiments with animals, some ingestion may also occur from inhalation exposures by mucociliary clearance or from animal grooming. The primary form of cadmium in occupational exposures is cadmium oxide. Experimental studies in laboratory animals have used cadmium oxide, cadmium chloride, and occasionally

other forms of cadmium such as cadmium sulfide and cadmium sulfate. In general, the different forms of cadmium have similar toxicological effects by the inhalation route although quantitative differences may exist from different absorption and distribution characteristics, particularly for the less soluble cadmium pigments such as cadmium sulfide and cadmium selenium sulfide (Buckley and Bassett 1978b; Klimisch 1993; Oldiges and Glaser 1986; Oldiges et al. 1989; Rusch et al. 1986).

Smokers inhale cadmium, but studies of cadmium exposure in the general population are considered in Section 2.2.2 because the primary route of exposure for the general population is through the diet. Also, the many other toxic compounds in cigarette smoke make it difficult at the present time to attribute specific adverse effects of smoking to the inhalation of cadmium.

2.2.1.1 Death

Numerous studies have shown that acute inhalation exposure to cadmium can cause death in humans and animals. In humans, several fatal inhalation exposures have occurred in occupational accidents. During the acute exposure, the general symptoms are relatively mild but, within a few days following exposure, severe pulmonary edema and chemical pneumonitis develop, leading to death due to respiratory failure (Beton et al. 1966; Lucas et al. 1980; Patwardhan and Finckh 1976; Seidal et al. 1993). The cadmium concentration in air was not measured in these cases of accidental death in humans. However, the lung concentrations of cadmium in the men who died from these accidental acute exposures were measured. I n micrograms of cadmium per gram wet weight (w/w) of lung tissue μg/g) Patwardhan and Finckh (1976) reported 1.5 μg/g, Beton et al. (1966) reported 2.5 μg/g, Barrett et al. (1947) reported 3.5 μg/g, and Lucas et al. (1980) reported 4.7 μg/g. Based upon estimates of the percentage of inhaled cadmium fume that would be retained in the lungs, Barrett et al. (1947) calculated an exposure of 2,500 min x mg/m^3 in air would be fatal to humans. Beton et al. (1966) used a similar technique to estimate that an exposure to CdO in air of 8.63 mg/m^3 for 5 hours led to the fatal deaths of the 5 workers with cadmium lung burdens of 2.5 μg/g. The lower lung concentrations reported by Patwardhan and Fin&h (1976) prompted Elinder (1986b) to estimate that an exposure of l-5 mg/m^3 for 8 hours could be immediately dangerous. These estimates of air concentrations, however, are based on a number of uncertain assumptions concerning the duration of exposure and the retention of cadmium in the human lung being similar to that found in animal studies (Barrett et al. 1947; Elinder 1986b). No studies on deaths in humans from intermediate inhalation exposures were found. In a study on chronic exposures, Friberg (1950) attributes the deaths of 2 workers to exposure to cadmium dust in the air averaging 6.8 mg Cd/m^3 (range 3-15 mg/m^3). One worker was

57 years old at death (after 14 years of exposure to the dust) and the other was 60 years old at death (after 25 years of exposure to the dust). A detailed post-mortem evaluation for the 60-year-old worker showed the presence of emphysema and the occurrence of hyaline casts in renal tubules, as well as slight nephrotic changes. Pneumonia was the direct cause of death as an acute complication of chronic bronchitis and pulmonary emphysema. The exposure estimate of 6.8 mg Cd/m^3 is from only 6 samples taken in 1946. The conditions in earlier years were thought to be similar, but this exposure value is, at best, a very rough approximation of the actual exposures spanning 34 years.

Acute inhalation of cadmium oxide fumes has also led to death in rats, mice, rabbits, guinea pigs, dogs, and monkeys, with the mortality rate apparently being directly proportional to the product of the duration of exposure and the concentration of inhaled cadmium (Barrett et al. 1947). The most reliable LC_{50} (lethal concentration, 50% kill) (at 7 days) established by this study was 500 min-mg CdO/m^3 for rats, equivalent to a 15minute exposure to 30 mg Cd/m^3 (Barrett et al. 1947). Rusch et al. (1986) demonstrated high mortality rates in the Sprague-Dawley rat from a 2-hour exposure to cadmium fumes at 112 mg Cd/m^3 (25 of 32 died within one week). A 2-hour exposure to a different form of cadmium, cadmium carbonate, at 132 mg Cd/m^3 resulted in considerably lower mortality (3 of 22 died by day 30). No deaths resulted from a 2-hour exposure to cadmium sulfide at 99 mg Cd/m^3 or cadmium selenium sulfide (cadmium red pigment) at 97 mg Cd/m^3. Grose et al. (1987) reported 2 out of 36 rats died from a 2-hour, nose-only inhalation exposure to only 0.45 mg Cd/m^3 of cadmium oxide dusts, but the statistical significance of this low rate of mortality was not reported. A 3-day, l-hour per day exposure to cadmium chloride aerosol at 61 mg Cd/m^3 resulted in the death of 17 of 18 rats exposed (Snider et al. 1973). In another study, no deaths were observed in rats from a cadmium yellow (CdS) pigment exposure for 10 days, 6 hours a day at 6.29 mg Cd/m^3 (Klimisch 1993). Thus, it appears that in acute exposures, the relatively more soluble cadmium chloride, cadmium oxide fume, and cadmium carbonate compounds are more toxic than the relatively less soluble cadmium sulfide compounds (Klimisch 1993; Rusch et al. 1986). Rusch et al. (1986) attribute this difference to higher lung absorption and retention times for the more soluble compounds, and greater mucociliary clearance for the less soluble pigments. Glaser et al. (1986), however, demonstrated that toxicity does not strictly correlate with solubility, and that solubility of cadmium oxide in biological fluids may be greater than its solubility in water. In hamsters, Henderson et al. (1979) reported that a 30minute exposure to 10.1 mg Cd/m^3 from $CdCl_2$ resulted in the death of 3 of 30 animals by day 6 postexposure. In rabbits, Friberg (1950) reported an LC_{50} (by day 14) from a 4-hour exposure to cadmium metal dusts at 28.4 mg Cd/m^3. Barrett et al. (1947) also reported LC_{50} values for cadmium oxide fume of 940 mg Cd/m^3 for a 14minute exposure in the monkey, 46.7 mg/m^3 for a 15-minute exposure in the mouse, 204 mg

Cd/m^3 for a 15minute exposure in the guinea pig, and 230 mg Cd/m^3 for a 15-minute exposure in the dog. However, the authors report that these LC_{50} values are only approximations because of insufficiencies in the data or the small numbers of animals used.

At longer durations of exposure, lower concentrationscause lethality in rats. Cadmium oxide dust resulted in the deaths of 100% of the females at 1 mg Cd/m^3 for 20 weeks, 5 days a week for 5 hours a day (Baranski and Sitarek 1987), and of 5 of 12 female rats at only 0.105 mg Cd/m^3 for 63 days, 7 days a week for 22 hours a day (Oldiges and Glaser 1986). Continuous inhalation exposure to cadmium oxide dust at 0.105 mg Cd/m^3 (i.e., 24 hours a day) for 63 days resulted in 5 of 12 deaths in female rats (Prigge 1978a). Five of 54 males died from a cadmium chloride exposure to 1.06 mg Cd/m^3 for 62 days, 5 days a week, 6 hours a day (Kutzman et al. 1986). Kutzman et al. (1986) determined that the concentration times hours of exposure to produce 50% mortality in rats was 390 mg-hr/m^3 (males) and 489 mg-hr/m^3 (females). Takenaka et al. (1983) reported that cadmium chloride at 0.0508 mg Cd/m^3 for 18 months, 7 days a week, 23 hours a day resulted in the death of 5 of 40 male rats.

Oldiges et al. (1989) evaluated the long-term effects in rats of inhaling cadmium as either $CdCl_2$, CdS04, CdS, or CdO. Rats were exposed to aerosols in nearly continuous exposures of 22 hours a day, 7 days a week, for 18 months. An observation period of 12 months followed the exposure period. Oldiges et al. (1989) recorded mortality as exceeding 25% of the test animals during the exposure period or 75% of the test animals during the observation period. If either 25 or 75% mortality occurred, the exposure period or the observation period, respectively, was terminated. The results showed that cadmium chloride at 0.030 mg Cd/m^3 was lethal to over 75% of the male and female rats by 12 months of exposure; cadmium oxide dusts at 0.090 mg Cd/m^3 were lethal for more than 25% of the males by 7 months and 25% of the females by 11 months of exposure; cadmium oxide fume at the highest dose of 0.03 mg Cd/m^3 did not result in >25% mortality during exposure or 75% during the postexposure period; cadmium sulfate at 0.090 mg Cd/m^3 was lethal for more than 25% of the males during the exposure and for more than 75% of the females by 14 months of following exposure; and cadmium sulfide at 0.090 mg Cd/m^3 was not lethal during the exposure period but was lethal to more than 75% of the males and females by 12 months postexposure. In these chronic studies, cadmium's lethal effects differed among the chemical forms in the following order from most to least toxic: $CdCl_2 > CdSO_4 \approx$ CdO dust>CdS, but lethality still occurred from all forms of cadmium. Oldiges and Glaser (1986) report that in their chronic studies and at the doses tested, cadmium toxicity appeared to be more related to the long-term lung retention of the bioavailable amounts of cadmium than to a simple function of solubility in water. Representative LOAEL and LC_{50}

values for lethality in each species and duration category are recorded in Table 2-1 and are plotted in Figure 2-1.

2.2.1.2 Systemic Effects

Representative NOAEL and LOAEL values for systemic effects following inhalation exposure to cadmium in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

Respiratory Effects. In humans, inhalation exposure to high levels of cadmium oxide fumes or dust is intensely irritating to respiratory tissue, but symptoms can be delayed. During and immediately after (up to 2 hours) an acute exposure for 5 hours of 8.63 mg/m^3, Beton et al. (1966) reported there were few symptoms of toxicity limited to coughing and slight irritation of the throat and mucosa. From 4 to 10 hours postexposure, influenza-like symptoms began to appear, including cough, tight chest, pain in chest on coughing, dyspnea, malaise, ache, chilling, sweating, shivering, and aching pain in back and limbs. From 8 hours to 7 days postexposure, more advanced stages of pulmonary response included severe dyspnea and wheezing, chest pain and precordial constriction, persistent cough, weakness and malaise, anorexia, nausea, diarrhea, nocturia, abdominal pain, hemoptysis, and prostration. Acute, high-level exposures can be fatal (see Section 2.2.1. I), and those who survive may have impaired lung function for years after a single acute exposure. A 34-year-old worker exposed to cadmium fume from soldering for 1 hour (dose not determined) had persistent impaired lung function when examined 4 years following the exposure (Barnhart and Rosenstock 1984). Initial symptoms were dyspnea, cough, myalgia, and fever. An initial chest X-ray revealed infiltrates. Townshend (1982) reports the case of a male welder who developed acute cadmium pneumonitis from a single exposure (dose not determined). Nine years after the exposure, this worker continued to show signs of progressive pulmonary fibrosis and had no improvement in respiratory function. Precise estimates of cadmium concentrations leading to acute respiratory effects in humans are not currently available.

The initial symptoms of respiratory distress observed in the higher acute exposures do not occur following lower-level, longer-term inhalation exposures (Friberg 1950). Longer-term occupational exposure to levels of cadmium below those causing lung inflammation, however, have been reported to cause emphysema and dyspnea in humans (Bonnell 1955; Friberg 1950; Lane and Campbell 1954; Smith et al. 1960). Kjellstrom

Table 2-1. Levels of Significant Exposure to Cadmium - Inhalation

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
ACUTE EXPOSURE							
Death							
1	Human	5 hr				8.63 M (5 male workers died after a 5 hour exposure)	Beton et al. 1966 CdO fume
2	Rat (NS)	10-15 min				30 (LC_{50} at 7 days)	Barrett et al. 1947 CdO fume
3	Rat (Sprague-Dawley)	2 hr				132 (3/22 died by day 30)	Rusch et al. 1986 CdCO3
4	Rat (Sprague-Dawley)	2 hr				112 (25/32 died within 1 week)	Rusch et al. 1986 CdO fume
5	Rat (Sprague-Dawley)	3 d 1 hr/d				61.0 M (17/18 died within 3 days)	Snider et al. 1973 $CdCl_2$
6	Hamster (Golden Syrian)	30 min				10.1 (3/30 died by day 6 postexposure)	Henderson et al. 1979 $CdCl_2$
7	Rabbit (NS)	4 hr				28.4 (LC_{50} at 14 days)	Friberg 1950 Cd metal dust
Systemic							
8	Human	5 hr	Resp			8.63 M (pulmonary edema and alveolar squamous cell metaplasia)	Beton et al. 1966 CdO fume
			Renal			8.63 M (bilateral cortical necrosis of kidneys)	

Table 2-1. Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
9	Rat (Long- Evans)	1 hr	Resp			5 M (pulmonary edema, enzyme changes associated with type 2 cell hyperplasia)	Boudreau et al. 1989 $CdCl_2$
10	Rat (Wistar)	3 hr	Resp		0.4 M (mild hypercellularity at the bronchoalveolar junction and in adjacent alveoli)	4.6 M (persistent focal interstitial thickening, increased collagen, general hypercellularity)	Buckley and Bassett 1987b CdO dust
			Bd Wt	0.4 M	4.6 M (15% decreased body weight)		
11	Rat (Sprague-Dawley)	1 hr	Resp			6.5 M (severe pneumonitis)	Bus et al. 1978 $CdCl_2$
			Bd Wt		6.5 M (10.8% decreased body weight)		
12	Rat (Sprague-Dawley)	2 hr	Resp	0.45 M		4.5 M (moderate to severe pneumonitis, hemorrhage, edema)	Grose et al. 1987 $CdCl_2$
			Bd Wt			4.5 M (20% decreased body weight)	
13	Rat (Sprague-Dawley)	2 hr	Resp		0.45 M (significant increased absolute and relative lung weight)	4.5 M (severe pneumonitis, hyperplasia of type 2 cells and fibroblasts)	Grose et al. 1987 CdO dust
			Bd Wt	0.45 M			
14	Rat (Lewis)	1-6 wk 5 d/wk 3 hr/d	Resp			1.6 M (interstitial pneumonitis)	Hart 1986 CdO dust
15	Rat (Lewis)	3 hr	Resp			8.4 M (diffuse alveolitis, with hemorrhage, edema, and sheets of mononuclear cells)	Hart et al. 1989a CdO dust

Table 2-1. Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL mg/m3	LOAEL Less serious mg/m3	LOAEL Serious mg/m3	Reference Chemical Form
16	Rat (Wistar)	10 d 6 hr/d	Resp		0.17 M (16% increased absolute lung weights)		Klimisch 1993 $CdCl_2$
			Renal	0.17 M			
			Bd Wt	0.17 M			
17	Rat (Wistar)	10 d 6 hr/d	Resp	0.72 M	6.29 M (8% increased absolute lung weight)		Klimisch 1993 CdS
			Renal	6.29 M			
			Bd Wt	6.29 M			
18	Rat (Sprague-Dawley)	2 hr	Resp			6.0 M (alveolar type 1 cell damage and necrosis)	Palmer et al. 1986 $CdCl_2$
			Endocr	6.0 M			
			Bd Wt	6.0 M			
19	Rat (Sprague-Dawley)	2 hr	Resp			132 (rales, rapid breathing, 2-3 fold increased lung weight)	Rusch et al. 1986 *CdCO3*
			Gastro		132 (erosions of the stomach)		
			Hepatic		132 (liver discoloration)		
			Bd Wt		132 (slower rate of weight gain)		
20	Rat (Sprague-Dawley)	2 hr	Resp			112 (labored breathing, rales, discoloration of lungs)	Rusch et al. 1986 CdO fume
			Hepatic		112 (liver discoloration and congestion)		
			Bd Wt		112 (excessive weight loss, percent not reported)		
21	Rat (Sprague-Dawley)	2 hr	Resp	99			Rusch et al. 1986 CdS
			Bd Wt	99			

Table 2-1. Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
22	Rat (Sprague-Dawley)	2 hr	Resp	97			Rusch et al. 1986 CdSeS
			Renal		97 (kidney discoloration)		
			Bd Wt	97			
23	Rat (Sprague-Dawley)	5, 10, or 15 d 1 hr/d	Resp			6.1 M (emphysema)	Snider et al. 1973 $CdCl_2$
24	Rat (Sprague-Dawley)	3 d 1 hr/d	Resp			61 M (pulmonary hemorrhage)	Snider et al. 1973 $CdCl_2$
25	Hamster (Golden Syrian)	30 min	Resp		1.1 (moderate increase in PMN, 2-fold increase in acid phosphatase)	10.1 (severe pneumonitis)	Henderson et al. 1979 $CdCl_2$
26	Rabbit (New Zealand)	2 hr	Resp		4.5 M (mild, multifocal interstitial pneumonitis)		Grose et al. 1987 $CdCl_2$
27	Rabbit (New Zealand)	2 hr	Resp		0.45 M (increase in alveolar macrophages)	4.5 M (multifocal interstitial pneumonitis)	Grose et al. 1987 CdO dust
			Bd Wt		0.45 M (unspecified decrease in body weight)		
Immunological/Lymphoreticular							
28	Mouse (Swiss)	2 hr		0.110 F	0.190 F (decreased humoral immune response)		Graham et al. 1978 $CdCl_2$
29	Mouse (C57Bl/6)	60 min			0.88 F (reduction in spleen lymphocyte viability [35%], numbers, and humoral response (75%)]		Krzystyniak et al. 1987 $CdCl_2$

Table 2-1. Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
	Neurological						
30	Rat (Sprague-Dawley)	2 hr				132 (tremors)	Rusch et al. 1986 CdCO3
31	Rat (Sprague-Dawley)	2 hr			112 (reduced activity)		Rusch et al. 1986 CdO fume
	INTERMEDIATE EXPOSURE						
	Death						
32	Rat (Wistar)	20 wk 5 d/wk 5 hr/d				1.0 F (13/13 died by week 20)	Baranski and Sitarek 1987 CdO dusts
33	Rat (Fischer 344)	62 d 5 d/wk 6 hr/d				1.06 M (5/54 males died)	*Kutzman et al.* 1986 $CdCl_2$
34	Rat (Wistar)	218-343 d 7 d/wk 22 hr/d				0.090 M (6/20 males died [CdO dust])	Oldiges and Glaser 1986 CdO dust CdO
						0.081 F (6/20 females died [CdO dust])	
35	Rat (Wistar)	6 mo 40 hr/wk				0.090 (> 75% mortality by 11-12 months postexposure)	Oldiges et al. 1989 $CdCl_2$
36	Rat (Wistar)	6 mo 40 hr/wk				0.270 (> 75% mortality by 21-23 months postexposure)	*Oldiges et al. 1989* CdS
37	Rat (Wistar)	63d 24 hr/d				0.105 F (5/12 died)	Prigge 1978a CdO dust

Table 2-1. Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
Systemic							
38	Rat (Wistar)	20 wk 5 d/wk 5 hr/d	Bd Wt	0.16 F		1.0 F (30-50% decreased body weight gain)	Baranski and Sitarek 1987 CdO dusts
39	Rat (Wistar)	30 d 7 d/wk 22 hr/d	Resp		0.105 M (increased total bronchoalvelolar macrophage numbers, leukocytes, and macrophage cytotoxicity)		Glaser et al. 1986 $CdCl_2$
			Hemato		0.105 M (45% increase in WBC)		
			Hepatic	105 M			
			Renal	105 M			
40	Rat (Wistar)	30 d 7 d/wk 22 hr/d	Resp		0.098 M (increased total bronchoalvelolar macrophage numbers, leukocytes, and macrophage cytotoxicity)		Glaser et al. 1986 CdO dust
			Hemato		0.098 M (45% increase in WBC)		
			Hepatic		0.098 M (increased ALT activity)		
			Renal		0.098 M (increased urinary creatinine)		
41	Rat (Wistar)	30 d 7 d/wk 22 hr/d	Resp		1.034 M (increased total bronchoalvelolar macrophage numbers, leukocytes, and macrophage cytotoxicity)		Glaser et al. 1986 CdS
			Hemato	1.034 M			
			Hepatic	1.034 M			
			Renal	1.034 M			
			Bd Wt	1.034 M			

Table 2-1. Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
42	Rat (Lewis)	5-6 wk 5 d/wk 3 hr/d	Resp			1.6 M (41% increased lung dry weight, type 2 cell hyperplasia)	Hart et al. 1989a CdO dust
43	Rat (Fischer 344)	62 d 5 d/wk 6 hr/d	Resp		0.33 M (bronchiolar hyperplasia, increase in fibroblasts and some collagen deposition)	1.06 M (fibrosis with significant increase in collagen)	Kutzman et al. 1986 $CdCl_2$
			Cardio	0.33 M	1.06 M (26% increased relative heart weight)		
			Hepatic	0.33 M	1.06 M (8% increased relative liver weight)		
			Renal	0.33 M	1.06 M (22% increased relative kidney weight)		
			Bd Wt	0.33	1.06 (14% decreased body weight)	2.13 (42% (female) to 51% (male) decreased body weight)	
44	Rat (Fischer 344)	4 wks 5 d/wk 6 hr/d	Resp	0.100 M			Oberdorster et al. 1994 $CdCl_2$
45	Rat (Wistar)	63 or 90 d 24 hr/d	Resp		0.025 F (hypercellularity in the bronchoalveolar region, increased lung relative weight)	0.105 (emphysema, histiocytic cell granulomas)	Prigge 1978a CdO dust
			Hemato		0.052 F (increased hemoglobin and hematocrit)		
			Hepatic	0.105 F			
			Renal	0.105 F			
			Bd Wt		0.105 F (11% decrease in body weight)		
			Metab		0.105 F (decreased blood pH and pO2, increased pCO2)		

Table 2-1. Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
46	Rat (Wistar)	21 d Gd 1-21 24 hr/d	Resp		0.204 F (77% increased lung relative weight)	0.581 F (for nonpregnant females: emphysematous areas, 2-fold increased wet lung relative weight, mild bronchiolitis)	Prigge 1978b $CdCl_2$
			Hemato		0.204 F (8% increased hemoglobin, 5% increased hematocrit)		
			Hepatic	0.581 F			
			Renal	0.581 F			
			Bd Wt	0.394 F			
47	Rat (Wistar)	21 d Gd 1-21 24 hr/d	Resp		0.204 F (70% increased lung relative weight)	NS F (for pregnant females: emphysematous areas, 2-fold increased lung relative weight, mild bronchiolitis)	Prigge 1978b $CdCl_2$
			Hemato		0.581 F (increased hemoglobin [12%], hematocrit [12%], total biliurin [2-fold])		
			Hepatic	0.581 F			
			Renal	0.581 F			
			Bd Wt		0.394 F (12% decreased maternal weight gain)		
48	Mouse (BALB/c)	4 wks 5 d/wk 6 hr/d	Resp		0.100 M (increased neutrophils, LDH and beta-glucuronidase; pulmonary inflammation)		Oberdorster et al. 1994 $CdCl_2$
49	Rabbit (NS)	9 mo 21 d/mo 3 hr/d	Resp			4.0 (chronic pneumonia, emphysema)	Friberg 1950 Cd metal dust
			Hemato		4.0 (eosinophilia, lower hemoglobin)		
			Renal			4.0 (proteinuria)	

Table 2-1. Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
50	Rabbit (NS)	7 mo 23 d/mo 3 hr/d	Resp			5.6 (emphysema)	Friberg 1950 *Cd metal dust*
			Renal			5.6 (proteinuria in 6/10 surviving to the end of exposure)	
51	Rabbit (NS)	4-6 wk 5 d/wk 6 hr/d	Resp			0.4 M (lung interstitial inflammation, type 2 cell hyperplasia)	Johansson et al. 1984 $CdCl_2$
	Immunological/Lymphoreticular						
52	Rat (Fischer 344)	62 d 5 d/wk 6 hr/d				1.06 M (26% increased in spleen relative organ weight, lymphoid hyperplasia, microgranulomas)	Kutzman et al. 1986 $CdCl_2$
53	Rat (Wistar)	21 d Gd 1-21 24 hr/d			0.394 F (14% increased spleen relative weight)		Prigge 1978b $CdCl_2$
	Neurological						
54	Rat (Wistar)	30 d 7 d/wk 22 hr/d		0.105 M			Glaser et al. 1986 $CdCl_2$
55	Rat (Wistar)	30 d 7 d/wk 22 hr/d		0.098 M			Glaser et al. 1986 *CdO dust*
56	Rat (Wistar)	30 d 7 d/wk 22 hr/d		1.034 M			Glaser et al. 1986 CdS
57	Rat (Fischer 344)	62 d 5 d/wk 6 hr/d		0.33 M	1.06 M (18% increased brain relative weight)		Kutzman et al. 1986 $CdCl_2$

Table 2-1. Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
Reproductive							
58	Rat (Wistar)	20 wk 5 d/wk 5 hr/d				1.0 F (increased duration of estrous cycle)	Baranski and Sitarek 1987 CdO dusts
59	Rat (Fischer 344)	62 d 5 d/wk 6 hr/d			1.06 M (24% increased relative testes weight)		Kutzman et al. 1986 $CdCl_2$
Developmental							
60	Rat (Wistar)	4-5 mo 5 d/wk 5 hr/d			0.02 (delayed ossification; behavioral alterations)	0.16 (decreased pup viability)	Baranski 1985 CdO dusts
61	Rat (Wistar)	21 d Gd 1-21 24 hr/d			0.581 (9% decreased fetal body weight, 12% increase in fetal alkaline phosphatase)		Prigge 1978b $CdCl_2$
Cancer							
62	Rat (Wistar)	6 mo 40 hr/wk				0.09 (CEL: lung bronchioalveolar adenomas, adenocarcinomas, and squamous cell carcinomas)	Oldiges et al. 1989 $CdCl_2$
63	Rat (Wistar)	6 mo 40 hr/wk				0.09 (CEL: lung bronchioalveolar adenomas, adenocarcinomas, and squamous cell carcinomas)	Oldiges et al. 1989 CdO dust
64	Rat (Wistar)	6 mo 40 hr/wk				0.270 (CEL: lung bronchioalveolar adenomas, adenocarcinomas, squamous cell carcinomas)	Oldiges et al. 1989 CdS

Table 2-1. Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
CHRONIC EXPOSURE							
Death							
65	Human	1-34 yr 5 d/wk 8 hr/d				6.8 M (2 fatalities from 14 years or 25 years of exposure to Cd dust)	Friberg 1950 Cd dust
66	Rat (Wistar)	105-409 d 7 d/wk 22 hr/d				0.254 M (3/20 died) 0.263 F (2/20 died)	Oldiges and Glaser 1986 CdS
67	Rat (Wistar)	413-455 d 7 d/wk 22 hr/d				0.095 M (6/20 died) 0.092 F (1/20 died)	Oldiges and Glaser 1986 *CdSO4*
68	Rat (Wistar)	18 mo 7 d/wk 22 hr/d				0.03 M (> 75% mortality by 12 *months postexposure*)	Oldiges et al. 1989 $CdCl_2$
69	Rat (Wistar)	18 mo 7 d/wk 22 hr/d				0.09 (more than 25% died after 7 months [M] and 11 months [F] of exposure)	Oldiges et al. 1989 CdO dust
70	Rat (Wistar)	18 mo 7 d/wk 22 hr/d				0. 09 (>75% mortality after 12 months postexposure)	Oldiges et al. 1989 CdS
71	Rat (Wistar)	18 mo 7 d/wk 22 hr/d				0.09 M (>25% mortality by 14 months of exposure) 0.09 F (>75% by 11 *months* postexposure)	Oldiges et al. 1989 CdSO4
72	Rat (Wistar)	18 mo 7 d/wk 23 hr/d				0.0508 M (5/40 died)	Takenaka et al. 1983 $CdCl_2$

Table 2-1. Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
Systemic							
73	Human	4-24 yr 5 d/wk 8 hr/d	Resp	0.025			Edling et al. 1986 CdO fume
74	Human	30 yr 5 d/wk 8 hr/d	Renal	0.033		0.067 (pronounced proteinuria)	Elinder et al. 1985b CdO fume
75	Human	30 yr 5 d/wk 8 hr/d	Renal	0.0153 M		0.0379 M (100% incidence of proteinuria in the cohort exposed to this level for 21 years)	Falck 1983 CdO fume
76	Human	30 yr 5d/wk 8hr/d	Renal	0.017		0.023 (9.2% incidence of proteinuria)	Jarup et al. 1988 CdO dust
77	Human	30 yr 5 d/wk 8 hr/d	Renal	0.0367 M			Mason et al. 1988 form not specified
78	Human	30 yr 5 d/wk 8 hr/d	Renal	0.027			Thun et al. 1989 CdO dust or fume
79	Rat (Wistar)	413-455 d 7 d/wk 22 hr/d	Resp		0.092 (unspecified increased lung weight)		Oldiges and Glaser 1986 CdSO4
			Hepatic	0.095			
			Bd Wt	0.095			
80	Rat (Wistar)	18 mo 7 d/wk 23 hr/d	Resp			0.0134 M (adenomatous hyperplasia in the bronchoalveolar area)	Takenaka et al. 1983 $CdCl_2$
			Bd Wt	0.0508 M			

Table 2-1. Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
Immunological/Lymphoreticular							
81	Rat (Wistar)	413-455 d 7 d/wk 22 hr/d			0.092 (enlarged thoracic lymph nodes)		Oldiges and Glaser 1986 CdSO4
Cancer							
82	Human	6 mo-43 yr 7d/wk 8hr/d				0.100 M (CEL: 50-111 lung cancer deaths per 1000 workers; 45 year exposure)	Stayner et al. 1992 CdO dust or
83	Rat (Wistar)	18 mo 7 d/wk 22 hr/d				0.03 (CEL: lung bronchioalveolar adenomas, adenocarcinomas, and squamous cell carcinomas)	Oldiges et al. 1989 $CdCl_2$
84	Rat (Wistar)	18 mo 7 d/wk 22 hr/d				0.03 (CEL: lung bronchioalveolar adenomas, adenocarcinomas, and squamous cell carcinomas)	Oldiges et al. 1989 CdO dust
85	Rat (Wistar)	18 mo 7 d/wk 22 hr/d				0.03 (CEL: lung bronchioalveolar adenomas, adenocarcinomas)	Oldiges et al. 1989 CdO fume
86	Rat (Wistar)	18 mo 7 d/wk 22 hr/d				0.09 (CEL: lung bronchioalveolar adenomas, adenocarcinomas, and squamous cell carcinomas)	Oldiges et al. 1989 CdS
87	Rat (Wistar)	18 mo 7 d/wk 22 hr/d				0.09 (CEL: lung bronchio-alveolar adenomas, adenocarcinomas, squamous cell carcinomas)	Oldiges et al. 1989 CdSO4

Table 2-1. Levels of Significant Exposure to Cadmium - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL		Reference Chemical Form
					Less serious (mg/m3)	Serious (mg/m3)	
88	Rat (Wistar)	18 mo 7 d/wk 23 hr/d				0.0134 M (CEL: lung epidermoid carcinomas, adenocarcinomas, and mucoepidermoid carcinomas)	Takenaka et al. 1983 $CdCl_2$

[a]The number corresponds to entries in Figure 2-1.

ALT = alanine amino transferase; AST = aspartate aminotransferase; Bd Wt = body weight; CEL = cancer effect level; d = day(s); Endocr = endocrine; F = female; Gastro = gastrointestinal; Gd = gestational day; Hemato = hematological; hr = hour(s); LC_{50} = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); mo = month(s); NOAEL = no-observed-adverse-effect level; NS = not specified; PMN = polymorphonuclear leukocytes; Resp = respiratory; WBC = white blood cells; wk = week(s); yr = year(s)

Figure 2-1. Levels of Significant Exposure to Cadmium - Inhalation

Acute (≤14 days)

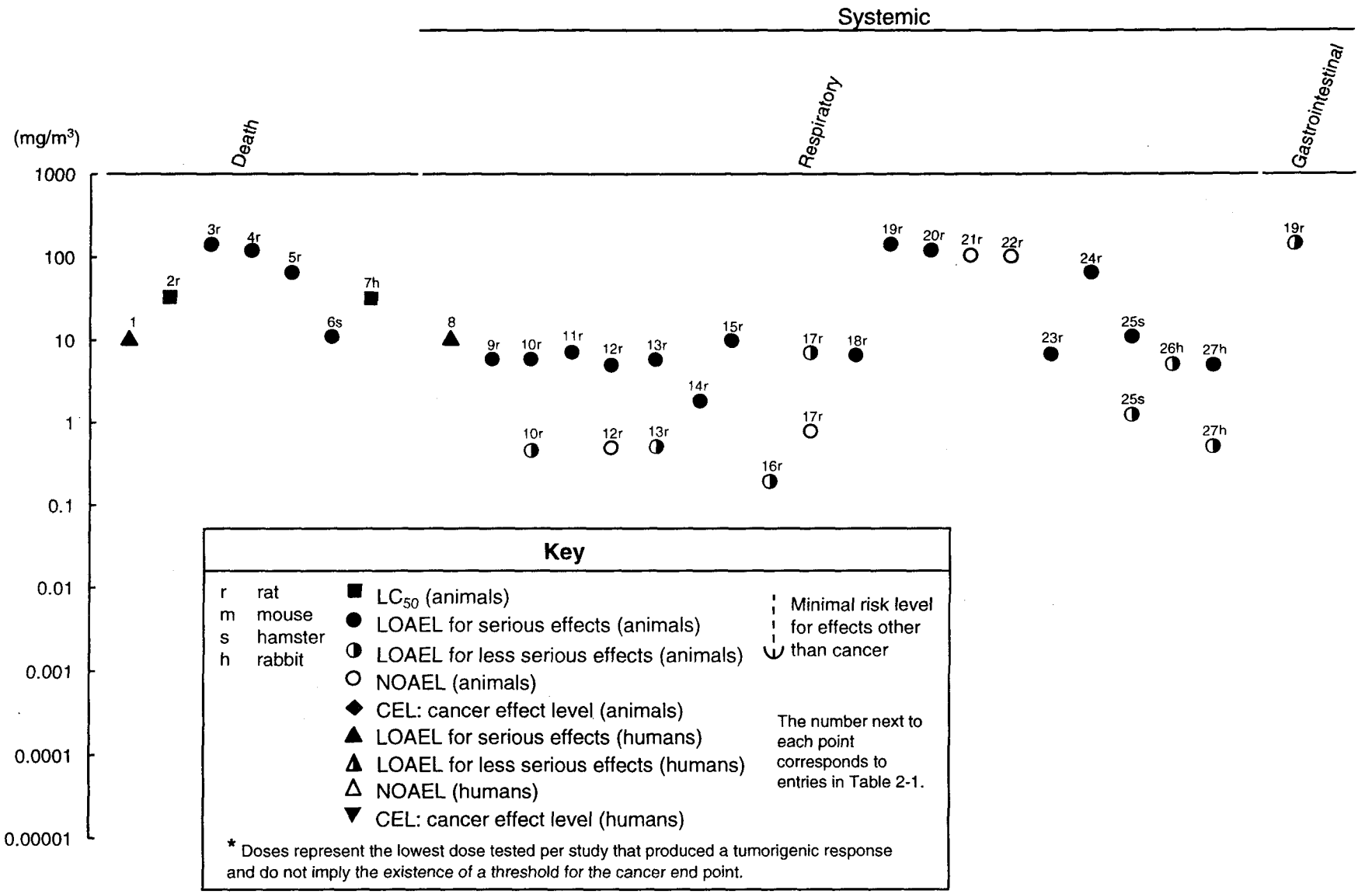


Figure 2-1. Levels of Significant Exposure to Cadmium - Inhalation (cont.)

Acute (≤14 days)

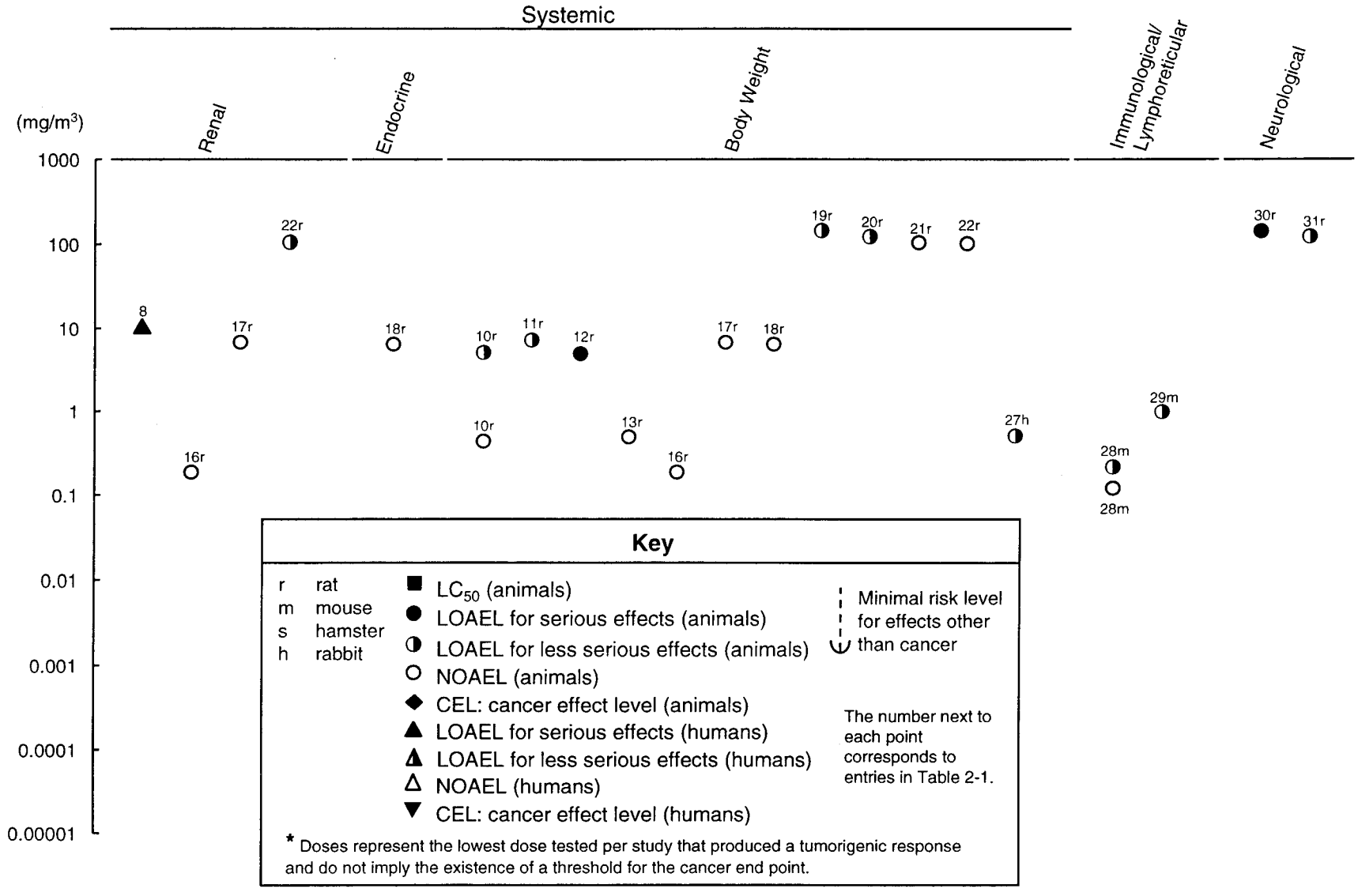


Figure 2-1. Levels of Significant Exposure to Cadmium - Inhalation (cont.)

Intermediate (15-364 days)

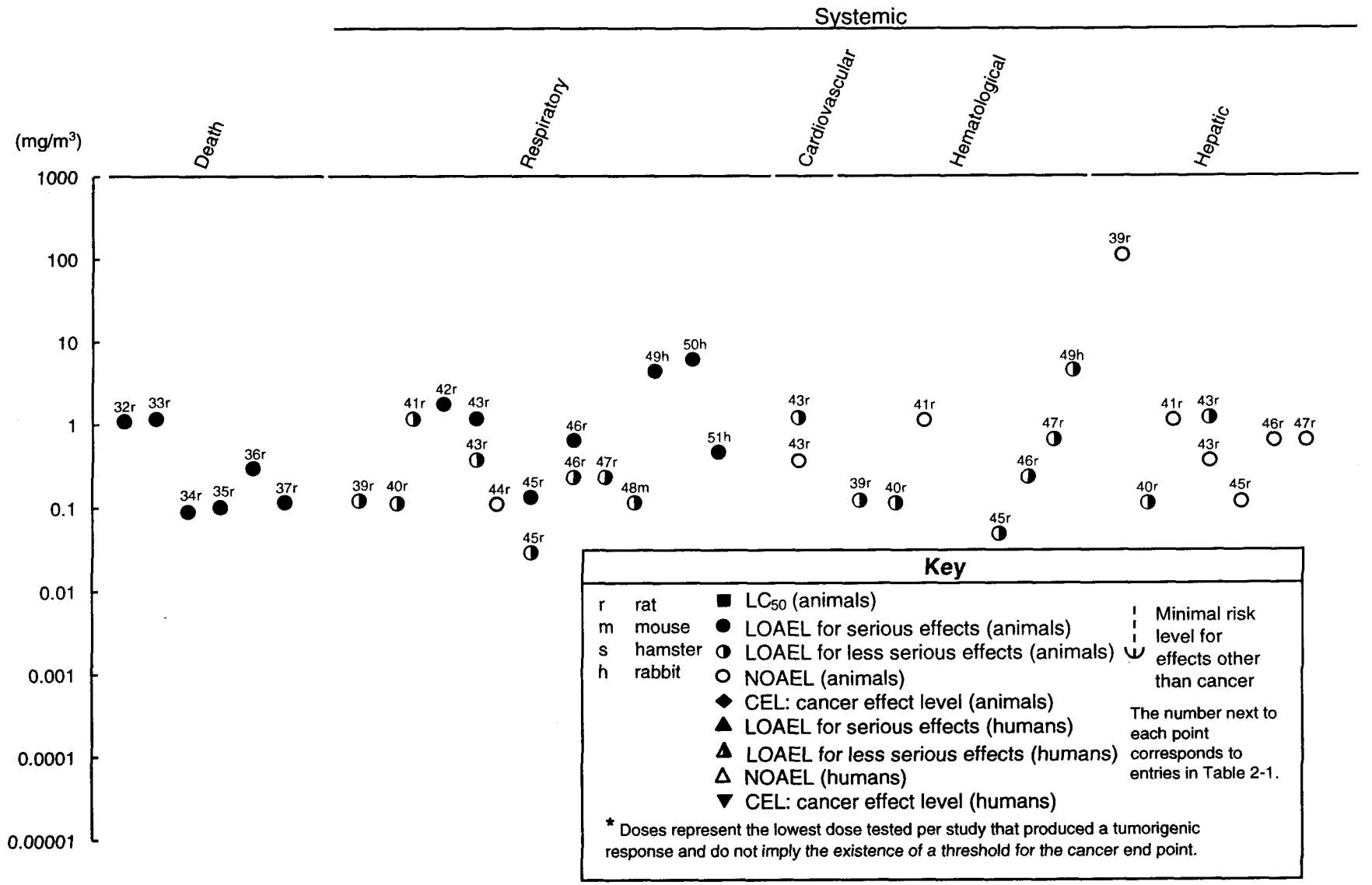


Figure 2-1. Levels of Significant Exposure to Cadmium - Inhalation (cont.)

Intermediate (15-364 days)

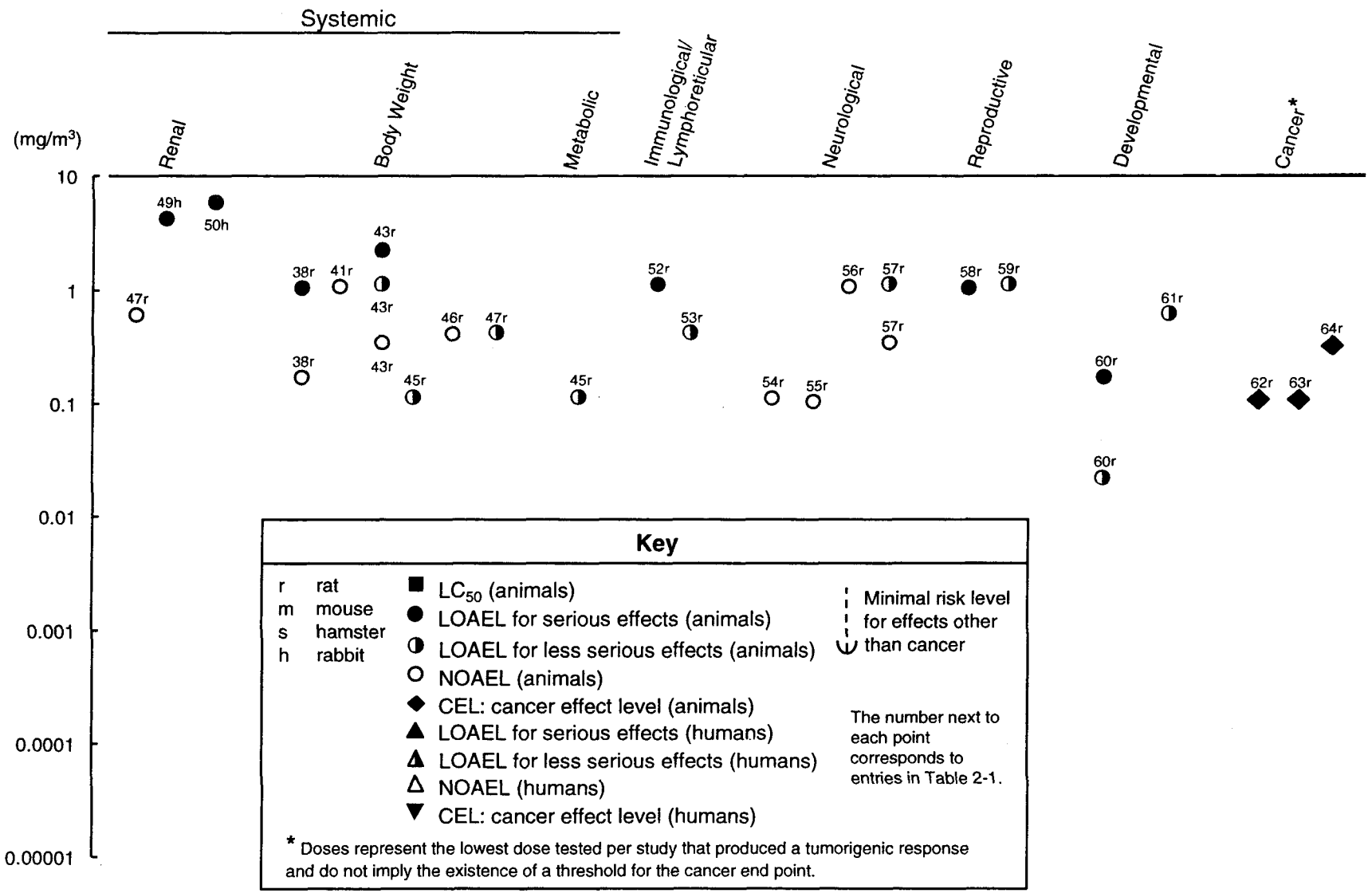
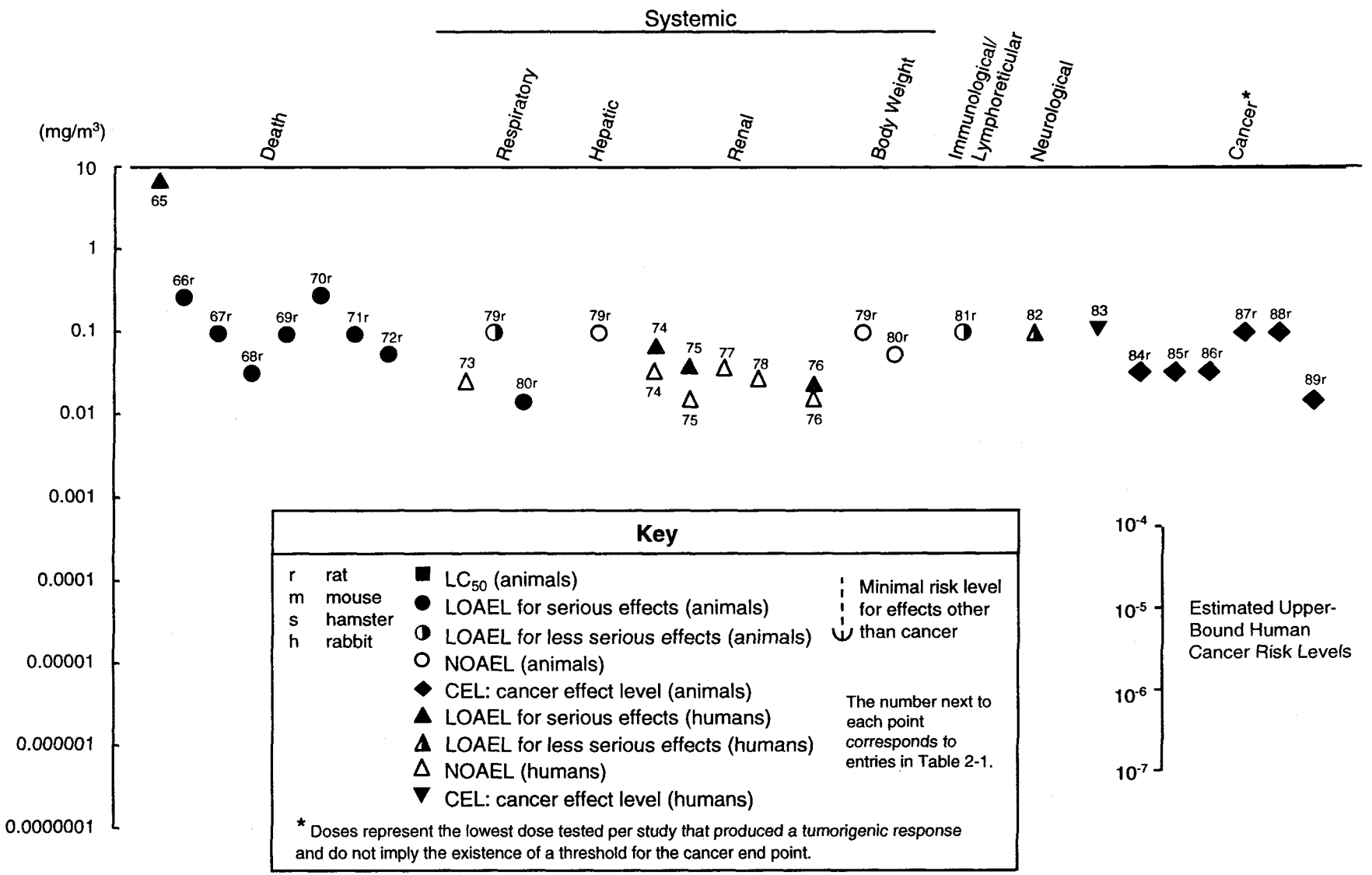


Figure 2-1. Levels of Significant Exposure to Cadmium - Inhalation (cont.)

Chronic (≥365 days)



et al. (1979) reported a significant increase in deaths due to respiratory diseases in cadmium-exposed battery factory workers exposed for longer than 5 years.

A significant, dose-dependent excess in the ratio of observed to expected deaths from bronchitis (i.e., Standardized Mortality Ratio=434) but not emphysema was found among 6,995 men occupationally exposed to cadmium for an average of 11 years (Armstrong and Kazantzis 1983). Dose level was not determined.

The earlier occupational studies did not control for the health effects of cigarette smoking. There is some evidence that cadmium may accelerate the development of emphysema in smokers. Leduc et al. (1993) report a case history of a 59-year-old male worker who smoked a pack of cigarettes per day since age 16, but had no prior history of respiratory disease in 1975 until developing emphysema in 1979 after inhaling various concentrations of cadmium (range of 0.0164-l.192 mg/m^3, mean of 0.446 mg/m^3, about nine times the threshold value of 0.050 mg/m^3) for 4 years as a furnace operator. Very high levels of cadmium in air samples at the workplace and in the patient's blood, urine, and lung tissue confirmed massive exposures. Lung-function tests declined rapidly, with a faster than usual onset of emphysema compared to other smokers. The mean concentration of cadmium in a removed section of lung was 580 μg/g dry tissue, compared to 14 μg/g in three unexposed controls matched for age, sex, and smoking habit who had also undergone resection of a bronchial carcinoma. The authors state that this case supports the hypothesis for an etiological role of cadmium fume inhalation in the development of emphysema.

More recent studies that controlled for smoking report lung impairment in cadmium-exposed workers (Chan et al. 1988; Cortona et al. 1992; Davison et al. 1988; Smith et al. 1976). Cortona et al. (1992) measured respiratory function parameters in 69 smoking and non-smoking male subjects (average age 45) who were exposed to concentrations of 0.008-l.53 mg/m^3 of cadmium fumes over a period of several years in a factory that produced cadmium alloys (silver-cadmium-copper). Forced Expiratory Volume (FEV), Forced Vital Capacity (FVC), Residual Volume (RV), Transfer Factor by the carbon monoxide method (TLCO), and Transfer Coefficient (KCO) were measured in these exposed individuals. The study found that there were no significant differences in the FVC, FEV, TLCO, and KCO between the workers exposed to cadmium fumes and control (non-exposed) individuals. There was a significant increase in RV of more than 8% in exposed workers; this effect was notably greater in those with higher cumulative exposures to cadmium (>l0%). It is uncertain how much of a factor on the increased RV was due to the tendency of smokers to develop an initial emphysematous alteration in lung tissue due to smoking.

Davison et al. (1988) evaluated lung function in 101 men who had manufactured copper-cadmium alloy in a plant in England for 1 or more years since 1926. The exposed men were compared to controls from the factory's other seven divisions matched for age and employment status. Smoking in exposed and control men was similar. Between 1951 and 1983, 933 measurements of airborne cadmium had been made, 697 with static samplers and 236 with personal samplers. The various sampling methods used before 1964 are no longer considered to be reliable, so estimates of air concentrations were made based on changes in production techniques, ventilation, levels of production, and discussions with occupational health physicians, industrial hygienist, the management, and the workers. Cadmium concentrations in air from 1926 to 1972 were determined to have declined from 0.6 to 0.156 mg/m^3. In 1973, concentrations were 0.085 mg/m^3; then from 1974 to 1983 concentrations ranged from 0.034-0.058 mg/m^3. The lung function of 77 of the men occupationally exposed to cadmium was significantly impaired compared to the unexposed controls, with the greatest abnormalities in the highest-dose group. Regression of the lung transfer coefficient versus cadmium exposure indicated a linear relationship with no apparent threshold.

Smith et al. (1976) studied the pulmonary function of 17 high-exposure workers, 12 low-exposure workers, and 17 controls. Cadmium air concentrations where high-exposure subjects worked were >0.2 mg/m^3. High-exposure subjects had worked at the plant a median of 26.4 years, with a maximum of 40.2 years, and low-exposure subjects had worked a median of 27.1 years, with a maximum of 34.8 years. Workers with high exposure to cadmium had significantly decreased the forced volume capacity (FVC) compared to low-exposure workers and controls. Chest X-rays indicated mild or moderate interstitial fibrosis in 29% of high exposure workers. A dose-response relationship was found between forced vital capacity and urinary cadmium, and with months of exposure to cadmium fume but not cadmium sulfate aerosol. In an analysis of the smoking habits, there was no significant difference between the two cadmium-exposed groups with respect to the proportion of present or past cigarette smokers, the intensity or duration of cigarette smoking, or cigar or pipe smoking habits. The control subjects, however, had a significantly ($p<0.05$) "higher" exposure to cigarette smoke than the cadmium exposed workers with substantially greater numbers of pack-years, cigarettes smoked per day, and years smoked. A step-down and multiple regression analyses with a dependent variable of FVC (as percent of predicted), and the independent variables, age-height, cigarette pack-years, and urinary cadmium, resulted in no indication that an interaction between the independent variables led to the observed relationship between FVC and cadmium excretion.

Other studies, however, have not shown a cadmium-related increase in impaired respiratory function. Edling et al. (1986) studied Swedish workers occupationally exposed to cadmium oxide (CdO) fume from

cadmium-containing solders. Cadmium-containing solder had been used at the plant from 1955 to 1978. The results from the lung-function analysis showed no significant difference in symptoms or lung function between the Cd-exposed and the reference group. The exposed and the reference groups were similar with respect to sex, age, and height. There was a higher percentage of smokers in the reference group (52%) than in the exposed group (42%), but the difference was not statistically significant. The authors could not explain why significant differences in effects were not seen in these workers since other studies have shown significant effects at comparable cadmium exposure levels. The authors suggest that a possible bias could have been introduced if people who had worked for more than 5 years in the plant had changed their occupation because of lung disease, so that only "healthy" workers remained. Significant effects may also have been found if the reference group included workers other than those who worked with solder, but the purpose of the study was to resolve the effects of cadmium exposure among workers with similar occupations. An analysis that factored out smoking by evaluating the data from smokers and nonsmokers separately also showed no significant impairment function between smoking exposed and smoking unexposed or nonsmoking exposed and nonsmoking unexposed. The lung impairment due to smoking was observed in that smokers in both the exposed and unexposed groups had a somewhat deteriorated closing volume and other lung function indicators in accordance with previous studies on the effects of smoking. These results support the hypothesis that the response to occupational dust exposure differs from the response to tobacco smoking.

Another possible reason for differing results is that lung injury caused by high-level cadmium exposure may be partially reversible (Bonnell 1955; Chan et al. 1988), with a return towards normal several years after exposures have been significantly reduced. Chan et al. (1988) studied a cohort of 36 female and 8 male workers at a Singapore cadmium battery factory exposed to cadmium oxide dust. Cadmium concentrations in air were 0.03-0.09 mg/m^3 (geometric means). Lung function was measured using spirometry, helium dilution, tidal sampling, X-ray, and respiratory symptoms. The recovery of lung function after reduction or cessation of occupational exposure to cadmium dusts was assessed. Total lung capacity increased following reduction of exposure and, following cessation of exposure, vital capacity, FEV, and prevalence of respiratory symptoms all improved. Blood and urine cadmium concentrations were considerably lower with the reduction or cessation of exposure and were consistent with a decrease in the cadmium air levels.

Additional respiratory symptoms less frequently reported in workers occupationally exposed to cadmium are chronic rhinitis and impairment or loss of the sense of smell (Adams et al. 1969; Bonnell 1955; Friberg

1950; Liu et al. 1985; Rose et al. 1992). The cause of these effects may be chronic irritation or necrosis of the nasal membranes, as they are generally found only in individuals with high-level exposure. An increased prevalence of abnormal parasinus radiographic findings in cadmium-exposed workers compared to other published reports on non-exposed populations was reported by Shaham et al. (1993).

Studies in animals confirm that inhalation exposure to cadmium can lead to respiratory injury. Single acute exposures in rats to cadmium oxide dust, cadmium oxide fume or cadmium chloride for l-5 hours in the 5-10 mg/m^3 range resulted in moderate to severe, multifocal interstitial pneumonitis, diffuse alveolitis with hemorrhage, increased lung weight, inhibition of macrophages, focal interstitial thickening, edema, and necrosis of alveolar type 1 cells leading to type 2 cell hyperplasia and fibroblasts (Boudreau et al. 1989; Buckley and Bassett 1987b; Bus et al. 1978; Grose et al. 1987; Hart et al. 1989a; Palmer et al. 1986). Similar results (i.e., severe pneumonitis) were seen in hamsters exposed to $CdCl_2$ at 10 mg/m^3 for 30 minutes (Henderson et al. 1979), and in rabbits exposed to CdO dusts at 4.5 mg/m^3 for 2 hours (Grose et al. 1987). Exposure to $CdCl_2$ at concentrations as low as 0.17 mg/m^3 for 6 hours a day for 10 days resulted in a 16% increase in absolute lung weight in rats (Klimisch 1993). Exposures in rats to $CdCl_2$ at 6.1 mg/m^3 1 hour a day for 5, 10, or 15 days, resulted in emphysema (Snider et al. 1973). Rats exposed to 61 mg/m^3 of $CdCl_2$ 1 hour a day for 3 days developed pulmonary hemorrhage (Snider et al. 1973). Rats exposed for 2 hours to $CdCO_3$ at the higher levels of 132 mg/m^3 developed rales, rapid breathing, and 2-3-fold increases in lung weight (Rusch et al. 1986). With the same dosing regimen, CdO fumes at 112 mg/m^3 resulted in rales, labored breathing, and lung discoloration in rats (Rusch et al. 1986).

The form of cadmium can affect its toxicity. Cadmium acetate, like cadmium chloride, produced severe respiratory effects from acute exposures in the l-5 mg/m^3 range. A single intra-tracheal instillation of cadmium acetate at 0.5 mg cadmium acetate/kg body weight (estimated to be 2.4 mg/m^3) has led to toxic lung lesions in the rat indicated by depressed levels of catalase and superoxide dismutase; increased nonprotein sulfhydryl content, glucose-6-phosphate dehydrogenase and glutathione peroxidase in lung tissue; and increases in lactate dehydrogenase (LDH) and protein in bronchoalveolar lavage fluid (BALF) (Salovsky et al. 1992). Exposure to cadmium sulfide at 6.29 mg/m^3 for 6 hours a day for 10 days resulted in an 8% increase in absolute lung weight in rats, compare to the 16% increased weight seen with only 0.17 mg/m^3 of cadmium chloride (Klimisch 1993). No respiratory effects were observed in rats exposed to cadmium sulfide at 99 mg/m^3 for 2 hours or to cadmium selenium sulfide at 97 mg/m^3 for 2 hours (Rusch et al. 1986).

Persistent damage has been reported in animal models from single acute exposure. Fibrosis caused by acute exposure was observed for at least 12 months postexposure (Dervan and Hayes 1979). Driscoll et al. (1992) evaluated rat alveolar macrophage fibronectin release, biochemical alterations in the BALF, and tumor necrosis factor (TNF) as early indicators of pulmonary inflammation in rats exposed once via intratracheal instillation to 0, 25, 100, or 400 μg $CdCl_2$/kg body weight. BALF was analyzed for LDH, total protein, and N-acetylglucosaminidase (NAG). Initial significant increases in BALF LDH, total protein, and NAG for all dose levels at day 3, and for all but LDH and NAG at the low-dose level at day 7, returned to control values by 28 days postexposure with one exception; total protein from the 400 μg/kg exposure remained elevated. The total protein response was dose-related. Neutrophils and lymphocyte numbers increased initially, but returned to control levels by days 14 and 28, respectively. In contrast, alveolar macrophage numbers increased after day 7, and remained elevated. While alveolar macrophage TNF did not change significantly, macrophage fibronectin release did significantly increase at all doses in a dose-related manner, and remained high through day 28. There was no statistically significant difference in cell viability for any of the cell populations. Hydroxyproline levels significantly increased at 100 and 400 μg/kg, but not at 25 μg/kg. Histopathological changes in the lung consisted of chronic interstitial inflammation characterized by increased alveolar wall thickening, increased number of mononuclear cells, type 2 cell hyperplasia, and at times, presence of brown pigment-laden macrophages. Alveolar spaces were variably collapsed with dilatation of some terminal bronchioles, alveolar ducts, and adjacent alveoli. The overall histopathological response was more severe at 90 days than at 28 days for the 100 and 400 μg/kg groups. Masson's trichrome-stained lung sections revealed minimally to moderately increased prominence of collagen, interpreted to reflect fibrosis in all dose groups; the response was dose related and more severe after 90 days than after 28 days.

Other studies report similar transient increases in BALF enzymes or other indicators of pulmonary pneumonitis, but also histopathological alterations that return to normal. Rats exposed to 1.6 mg/m^3 of CdO dust for 3 hours a day, 5 days a week for 1-6 weeks developed an interstitial pulmonary pneumonitis the first 2 weeks as indicated by changes in airway amounts of lactic dehydrogenase, alkaline and acid phosphatase, protein, and polymorphonuclear leukocytes. The levels of these biochemical and cytological indicators of toxicity, and the accompanying histopathological alterations, returned towards normal values during the next three weeks even though cadmium continued to accumulate in the lung. Hart (1986) suggests that the adaptive synthesis of a Cd-binding protein (i.e., presumptive metallothioneins) in the lung serves to sequester cadmium and protect the tissue from further toxicity.

Palmer et al. (1986) evaluated the role of thyroid hormone in the pulmonary repair process following $CdCl_2$-induced acute lung injury. Normal and thyroidectomized (Thyx) rats were exposed via inhalation for 2 hours to a 10 mg $CdCl_2/m^3$ aerosol. The unmodified euthyroid rats exposed to $CdCl_2$ exhibited primarily type 1 epithelial cell damage and necrosis with only minor morphological changes in type 2 cells. In contrast, thyroidectomy, followed by $CdCl_2$ exposure, produced earlier and more severe acute injury in the form of patchy alveolar edema, hemorrhage, and hyaline membrane formation on alveolar surfaces were common. Type 2 cell hyperplasia was markedly reduced compared to the euthyroid control. Type 2 cells in the Thyx rats also showed prominent cytoplasmic vacuolization, marked increase of the perinuclear space, and early nuclear alterations suggestive of pyknosis. The severity of the injury to type 2 cells in $CdCl_2$-exposed Thyx rats may account, in large measure, for the decreased DNA synthetic and proliferative ability of these cells, which would enhance the acute lung damage. Reductions in repair response were also seen in the number of lavageable lung cells (down 60% lower) and antioxidant enzyme activity (4.5-5% lower) than the normal rat response. Antioxidant enzymes were depressed especially in the early days postexposure. The authors suggest that depressed levels of T4 and increased oxidant damage may play a role in the underlying mechanism of increased damage seen in the Thyx rats. Thus, the persistence of lung damage or the development of further damage for a given level of acute exposure is probably related to the capacity of pulmonary repair mechanisms (e.g., type 2 cell hyperplasia) and to adaptive responses like the production of metal binding proteins to sequester free cadmium away from target sites.

Intermediate-duration exposure to cadmium results in similar respiratory effects as seen in the acute exposures. The level and duration of exposure determine the severity of the effects in a dose-response manner. Intermediate exposure levels in the 0.4-4 mg Cd/m^3 range generally result in serious lung damage. Kutzman et al. (1986) reported fibrosis with significant increase in collagen in rats exposed to $CdCl_2$ at 1.06 mg Cd/m^3 for 6 hours a day, 5 days a week for 62 days. Prigge (1978b) reported emphysema and bronchiolitis in pregnant rats exposed to $CdCl_2$ at 0.581 mg Cd/m^3 for 24 hours a day, for 21 days (gestational days [Gd] 1-21). Hart et al. (1989a) reported type 2 cell hyperplasia and a 41% increased lung dry weight in rats exposed to CdO at 1.6 mg Cd/m^3 for 3 hours a day, 5 days a week for 5-6 weeks. Friberg (1950) reported chronic pneumonia and emphysema in rabbits exposed to cadmium metal dust at 4 mg Cd/m^3 for 3 hours a day, 21 days a month for 9 months, and at 5.6 mg Cd/m^3 for 3 hours a day, 23 days a month for 7 months. Johansson et al. (1984) observed type 2 cell hyperplasia and lung interstitial inflammation in rabbits exposed to $CdCl_2$ at 0.4 mg Cd/m^3 for 6 hours a day, 5 days a week for 4-6 weeks. With longer exposure durations increasingly lower doses result in serious respiratory toxicity. Cadmium oxide dust, at doses as low as 0.105 mg Cd/m^3, has been shown to produce emphysema and

histiocytic cell granulomas in rats when administered for 24 hours a day for 62 days (exposure terminated due to high mortality) (Prigge et al. 1978a). At a lower dose of 0.025 mg Cd/m^3 for 24 hours a day for 90 days, CdO dust produced less severe toxicity including hypercellularity in the bronchoalveolar region and increased relative weight in the lung (Prigge et al. 1978a). Similar effects (i.e., bronchoalveolar hypercellularity) were seen for exposures to CdO dust at 0.098 mg Cd/m^3 for 22 hours a day, 7 days a week for 30 days; for exposures to $CdCl_2$ at 0.105 mg Cd/m^3 for 22 hours a day, 7 days a week for 30 days; and for exposures to CdS at 1.034 mg Cd/m^3 for 22 hours a day, 7 days a week for 30 days (Glaser et al. 1986). As with the acute exposures, cadmium sulfide is less toxic than cadmium oxide or cadmium chloride (Glaser et al. 1986).

Some tolerance to cadmium appears to develop with duration of dose so that lung lesions that developed after a few weeks of exposure are not seen to progress, sometimes even reversing after longer exposures (Hart 1986; Hart et al. 1989a). Multiple mechanisms appear to be responsible for this tolerance, including the synthesis of lung metallothionein (see Section 2.3.3) and an increase in type 2 cells (Hart et al. 1989a). With respect to differential response related to metallothionein, Oberdorster et al. (1994) compared the pulmonary responses of rats and mice to a long-term aerosol exposure of $CdCl_2$ at 100 μg Cd/m^3 6 hours a day, 5 days a week for 4 weeks. Parameters monitored included metallothionein, retained cadmium in the lung, BALF neutrophil counts, and enzyme activity (β-glucuronidase and LDH); cell proliferation measured by bromodeoxyuridine (BrdU) incorporation into lung tissues; lung morphology (histochemical staining), and induction of metallothionein concentration in lung tissue. The results showed that mice respond with significantly greater inflammatory response in their lungs after $CdCl_2$ exposure than do rats. Mice had a greater cell proliferative response, a higher baseline metallothionein level, lung metallothionein that is more inducible, and lung burdens of cadmium metallothionein that were twice as high as in rats from the same aerosol concentration of $CdCl_2$. Higher burdens are expected because of the higher respiratory rate in mice. Although the mice had increased cell proliferation, mice also responded with a significant induction of metallothionein in the epithelial cells of the conducting airways and alveolar region. Rats did not have this response. Increased metallothionein may provide more protection against the development of lung tumors in proliferating cells. The authors suggest that these enhanced responses in mice may contribute to the lack of pulmonary carcinogenicity found in mice. The authors also noted that an increased cell proliferative response (as seen in the mouse) does not necessarily lead to increased risk of tumor development, for it is the rat (with the lesser proliferative response) that is more prone to lung tumors from inhaled cadmium.

There are fewer chronic-inhalation exposure studies that specifically reported systemic respiratory effects. Oldiges and Glaser (1986) report increased lung weights (amount unspecified) in rats from exposure to either $CdSO_4$ at 0.092 mg Cd/m^3 or CdS at 0.254 mg Cd/m^3 for 22 hours a day, 7 days a week for 413-455 days. Takenaka et al. (1983) observed adenomatous hyperplasia in the bronchoalveolar region in rats from exposure to $CdCl_2$ at 0.0134 mg Cd/m^3 for 23 hours a day, 7 days a week for 18 months.

Cardiovascular Effects. Inhalation exposure to cadmium does not appear to have significant effects on the cardiovascular system. Most studies of workers occupationally exposed to cadmium have not found cadmium-related cardiovascular toxicity. In some studies, the mortality from cardiovascular disease was lower in the cadmium-exposed population. Armstrong and Kazantzis (1983) reported that a cohort of 6,995 British men occupationally exposed to cadmium for an average duration of 11 years had a significantly lower mortality from vascular disease.

Fifty-three male workers exposed to cadmium and lead and 52 male controls were examined for correlations in urine levels and blood pressure. The average duration of exposure was 12.5 years. Correlations between blood pressure and urinary cadmium in exposed workers were not significant after controlling for age or age and heart rate. Exposure to lead was a significant confounding factor (de Kort et al. 1987).

Friberg (1950) investigated the health of workers in a manufacturing plant that made cadmium-containing electrodes used in the production of batteries. Fifty-eight workers (30-50 years of age) were divided into 2 groups based on number of years at the plant. Workers were clinically examined for subjective symptoms and corresponding morphological or functional changes of the respiratory, cardiovascular, and excretory systems. The cardiovascular exam was largely unremarkable. Only a slight rise in blood pressure in a few cases was observed in Group 1. Electrocardiograms (EKG) were not significantly different from a matched control group in Group 1. Group 2 had neither increased blood pressure or altered EKGs.

Kazantzis et al. (1988) studied mortality in a cohort of 6,958 cadmium-exposed male workers with average occupational exposures of 12 years. This was a follow-up study to the work of Armstrong and Kazantzis (1983). There was a significant deficit in deaths from cerebrovascular disease among men occupationally exposed to cadmium. There was no significant excess risk from hypertensive or renal disease.

Smith et al. (1980) studied 16 male high-exposure production workers and 11 male low-exposure office and supervisory workers for renal function. Average duration of exposure was 25 years. High-exposure workers were exposed to CdO concentrations of 0.23-45.2 mg/m^3 and CdS concentrations of 0.04-l 27 mg/m^3. No difference was found in hypertension between high- and low-exposure workers, adjusted for age and weight or cigarette smoking.

Sorahan and Waterhouse (1983) examined mortality rates in a cohort of 3,025 nickel-cadmium battery workers (2,559 males and 466 females). Cadmium levels in air ranged from 0.05 to 2.8 mg/m^3, primarily as CdO. Duration of exposure ranged from 1 year to more than 6 years. No increase in mortality from diseases of the circulatory system (e.g., hypertension) were seen in cadmium-exposed workers.

Staessen and Lauwerys (1993), in a study known as the Cadmibel Study (a cross-sectional population study), evaluated 2,327 people from a random sample of the population of four Belgian districts chosen to provide a wide range of environmental exposure to cadmium. Participants completed a questionnaire regarding their medical history, current and past occupations, smoking habits, alcohol consumption, and intake of medications. Urine and blood samples were taken, and pulse rate, blood pressure, height, and weight were recorded. Exposure to cadmium was considered to be by both the oral and inhalation routes. Cadmium levels in blood and urine were significantly increased in the high-exposure areas compared to the low-exposure areas ($p<0.00l$). Blood pressure was not correlated with the urine or blood cadmium levels. The prevalence of hypertension or other cardiovascular diseases was similar in all four districts, and was not correlated with urine or blood cadmium levels. These results do not support a hypothesis that cadmium increases blood pressure, prevalence of hypertension, or other cardiovascular diseases.

One study found a statistically significant increase in blood pressure in exposed workers compared to controls (Thun et al. 1989), but mortality in this cohort was lower than expected (Thun et al. 1985). Only one study was found regarding cardiovascular effects in animals after inhalation exposure to cadmium. Kutzman et al. (1986) reported a significant increase in relative heart weight in rats exposed to 1.06 mg Cd/m^3 cadmium chloride for 62 days, 5 days a week 6 hours a day. Body weights in these rat were also significantly reduced from this exposure, and absolute organ weights were not reported, so the significance of this toxic effect on the heart is unclear.

Gastrointestinal Effects. In the cohort he studied, Friberg (1950) found no association between inhalation cadmium exposure in workers and symptoms of gastrointestinal toxicity. Symptoms that had been reported in case histories from the 1920s included pain or tenderness at the epigastrium associated with nausea and some constipation. No other human studies report any cadmium associated gastrointestinal toxicity from inhalation exposure.

In the only animal study located, Rusch et al. (1986) observed erosion of the stomach in rats from exposure to cadmium carbonate at 132 mg Cd/m^3 for 2 hours. Post-mortem evaluation was performed at 1, 3, 7, and 30 days postexposure. After the inhalation exposure in a whole-body chamber, rats were vacuumed to remove any CdCO, dust adhering to the ventral and dorsal fur. The 132 mg Cd/m^3 dose is relatively high. Three of the 10 test animals died during the 2-hour exposure so the significance of the gastrointestinal effect in this study is unclear.

Hematological Effects. The evidence concerning hematological effects following inhalation exposure to cadmium is conflicting. Lowered hemoglobin concentrations and decreased packed cell volumes have been observed in some studies of workers occupationally exposed to cadmium (Bernard et al. 1979; Friberg 1950; Kagamimori et al. 1986), but not in others (Bonnell 1955; Chan et al. 1988; Davison et al. 1988). The changes that were found often were not statistically significant (Bernard et al. 1979; Friberg 1950), and examination of bone marrow of some workers with lowered hemoglobin revealed no detectable abnormalities (Friberg 1950).

Conflicting results on the hematologic effect of cadmium after inhalation exposure have also been obtained with animal studies. Rabbits exposed to cadmium oxide dust at 4 mg/m^3 for 3 hours a day, 21 days a month for 9 months developed eosinophilia and a slightly lower hemoglobin (Friberg 1950). In contrast, rats exposed to CdO dust at 0.052 mg Cd/m^3 for 24 hours a day for 90 days had increased hemoglobin and hematocrit that were attributed to decreased lung function (Prigge 1978a). Prigge (I 978b) also reported increased hemoglobin and hematocrit in rats exposed to $CdCl_2$ at 0.204, 0.394, or 0.581 mg Cd/m^3 24 hours a day for 21 days. Other studies report no Cd-related hematological effects. A nearly continuous 30-day exposure in rats to CdS at 1.034 mg Cd/m^3 had no effect on red blood cell counts (Glaser et al. 1986). A nearly continuous 218-day exposure in rats to CdO dust or fume at 0.090 mg Cd/m^3 had no effect on a routine hematological evaluation (specific tests not reported) (Oldiges and Glaser 1986). A partial explanation for these conflicting results may be that Cd-induced anemia primarily results from

impaired absorption of iron from the diet following gastrointestinal exposure to cadmium (see Section 2.2.2.2), and the amount of gastrointestinal exposure following cadmium inhalation is variable depending on the form and dose.

Musculoskeletal Effects. Case studies indicate that calcium deficiency, osteoporosis, or osteomalacia can develop in some workers after long-term occupational exposure to high levels of cadmium (Adams et al. 1969; Blainey et al. 1980; Bonnell 1955; Kazantzis 1979; Scott et al. 1980). Effects on bone generally arise only after kidney damage has occurred and are likely to be secondary to resulting changes in calcium, phosphorus, and vitamin D metabolism (Blainey et al. 1980).

No studies were located regarding musculoskeletal effects in animals after inhalation exposure to cadmium.

Hepatic Effects. Liver effects are not usually associated with inhalation exposure to cadmium. Friberg (1950) reported some nonspecific signs of liver disease in some workers from a group exposed to cadmium in the air for 20 years. Test results included increased serum gamma-globulin, and other indicators of abnormal serum globulins, including the flocculation test results of a positive Takata reaction and/or an elevated thymol values. These tests (the latter of which are not used today) were nonspecific indicators of cirrhosis or hepatitis. The significance of these test results with respect to cadmium exposure is questionable. Subsequent studies on workers exposed to cadmium in the air have not reported adverse liver effects (Adams et al. 1969; Bonnell 1955).

Liver effects have occasionally been found in animal studies. Cats examined within one day of inhalation exposure to an unspecified concentration of cadmium oxide fume had a variety of hepatic lesions, and liver changes from cell granulation at low doses to fatty infiltration at high doses (Prodan 1932). Increased serum alanine aminotransferase activity, indicative of liver damage, was seen in rats exposed for 30 days to 0.1 mg/m^3 cadmium, but activity had returned to normal 2 months after exposure (Glaser et al. 1986). Kutzman et al. (1986) reported an increased liver relative weight in rats from a $CdCl_2$ exposure at 1.06 mg Cd/m^3 for 6 hours a day, 5 days a week, for 62 days. Increased liver weight was not observed from a continuous $CdCl_2$ exposure at 0.029 mg Cd/m^3 for 255 days, from a continuous CdO exposure at 0.090 mg Cd/m^3 for 218 days, or from a continuous CdSO, exposure at 0.095 mg Cd/m^3 for 413 days (Oldiges and Glaser 1986). Similar negative results were reported by Prigge (1978a, 1978b) for a 21-day exposure to $CdCl_2$ at 0.581 mg Cd/m^3, and for a 63-day exposure to CdO at 0.105 mg Cd/m^3 (a dose that was very

toxic to the lungs). A continuous high-dose exposure to CdS at 2.247 mg Cd/m^3 for 105 days did result in an unspecified increase in liver weight in surviving rats (Oldiges and Glaser 1986). Cadmium accumulates in the liver as well as the kidney, the main target organ for cadmium toxicity. The resistance of the liver to toxic effects from cadmium may be related to a higher capacity of the liver to produce metallothionein that would bind to cadmium and would lower the concentrations of free cadmium ions (see Section 2.3.3).

Renal Effects. There is very strong evidence that the kidney is the main target organ of cadmium toxicity following extended inhalation exposure to cadmium. The sensitivity of the kidney to cadmium was recognized in an early investigation of workers exposed to cadmium oxide dust and cadmium fumes in a factory producing nickel-cadmium batteries (Friberg 1950). These workers suffered from a high incidence of abnormal renal function, indicated by proteinuria and a decrease in glomerular filtration rate. Similar signs of renal damage have been observed in many other studies of workers occupationally exposed to cadmium (Adams et al. 1969; Beton et al. 1966; Bernard et al. 1979; Bonnell 1955; Bustueva et al. 1994; Chia et al. 1989; Elinder et al. 1985a, 1985b; Falck et al. 1983; Gompertz et al. 1983; Iwata et al. 1993; Jakubowski et al, 1987; Jarup and Elinder 1993; Jarup et al.; 1988 Kjellstrom et al. 1977a; Liu et al. 1985; Mason et al. 1988; Piscator 1966; Roels et al. 1981b; Rose et al. 1992; Smith et al. 1980; Thun et al. 1989).

The proteinuria caused by cadmium exposure is characterized by the presence of a number of low molecular-weight proteins in urine, including β_2-microglobulin, lysozyme, ribonuclease, immunoglobulin light chains, and retinol-binding protein (Piscator 1966). These low-molecular-weight proteins are all readily filtered by the glomerulus and are normally reabsorbed in the proximal tubules of the kidney. Elevated urinary excretion of these proteins is indicative of proximal tubular damage. Urinary excretion of high-molecular-weight proteins such as albumin has also been reported in occupationally exposed workers (Bernard et al. 1979; Elinder et al. 1985b; Mason et al. 1988; Roels et al. 1989; Thun et al. 1989), but there is some debate as to whether this represents glomerular damage (Bernard et al. 1979; Roels et al. 1989) or severe tubular damage (Elinder et al. 1985a; Mason et al. 1988; Piscator 1984).

The tubular proteinuria caused by cadmium exposure may be accompanied by depressed tubular resorption of other solutes such as enzymes, amino acids, glucose, calcium, copper, and inorganic phosphate (Elinder et al. 1985a, 1985b; Falck et al. 1983; Gompertz et al. 1983; Mason et al. 1988). It has been suggested that the urinary concentrations of some of these solutes, particularly renal enzymes, are more sensitive than low-molecular-weight proteins for detecting tubular dysfunction in exposed humans (see Section 2.5.2).

An additional effect on the kidney seen in workers after high levels of inhalation exposure to cadmium is an increased frequency of kidney stone formation (Elinder et al. 1985a; Falck et al. 1983; Kazantzis 1979; Scott et al. 1978; Thun et al. 1989). This effect is likely to be secondary to disruption of calcium metabolism due to kidney damage.

Tubular dysfunction generally develops only after cadmium reaches a minimum threshold in the renal cortex. This threshold is often referred to as the "critical concentration." Care must be taken in its interpretation because it is not invariant, but depends on a number of variables (Foulkes 1990). The critical concentration of cadmium in the renal cortex associated with increased incidence of renal dysfunction in an adult human population chronically exposed to cadmium has been estimated to be about 200 μg/g wet weight by several investigators (Friberg et al. 1974; Kjellstrom et al. 1977a, 1984; Roels et al. 1983).

Several quantitative evaluations of kidney toxicity have been performed using cumulative dose (exposure duration times cadmium concentration) as the independent variable. For presentation in Table 2-1 and Figure 2-1, a standard exposure period of 30 years has been used to convert reported units of mg-years/m^3 to mg/m^3, based on the assumption that uptake is a linear function of concentration and time. An early study found a 10% prevalence of proteinuria at an average 30-year exposure to cadmium oxide dust of 0.017 mg Cd/m^3 (Kjellstrom et al. 1977a), but a subsequent follow-up study found only a 4% prevalence at this level of exposure (Jarup et al. 1988). The definition of proteinuria used in these studies is an excretion exceeding the 95th percentile of a normal population. Thus, a prevalence of 5% or less was considered to be unrelated to cadmium exposure. Among the workers in the follow-up study, the prevalence of proteinuria was 1.1% in the lowest exposure group with a 30-year exposure to 0.00437 mg cadmium/m^3 and 9% at 0.023 mg/m^3 (Jar-up et al. 1988). Logistic regression generated a prevalence of 4% at a 30-year exposure to 0.017 mg/m^3, which was considered to be the NOAEL for this cohort. Other recent analyses have found 30-year thresholds for proteinuria of 0.027 mg/m^3 (Thun et al. 1989), 0.033 mg/m^3 (Elinder et al. 1985b), or 0.0367 mg/m^3 (Mason et al. 1988). In another cohort, with an average 30-year exposure to cadmium fume of 0.026 mg/m^3, the average exposures of workers with and without proteinuria were 0.038 and 0.015 mg/m^3, respectively (Falck et al. 1983).

Cessation of cadmium exposure generally does not lead to a decrease in proteinuria in occupationally exposed workers (Elinder et al. 1985b; Mason et al. 1988; Piscator 1984; Thun et al. 1989), possibly because the kidney cadmium level declines very slowly after cessation of exposure. Kidney damage may

continue to worsen after exposure ceases. A progressive reduction of the glomerular filtration rate in excess of the usual age-related decline was found in 23 workers 5 years after they were removed from cadmium exposure because of proteinuria and/or albuminuria (Roels et al. 1989). End-stage renal disease is not a common cause of death among workers occupationally exposed to cadmium, but it is significantly elevated over expected values in some occupational cohorts (Elinder et al. 198%; Kazantzis et al. 1988).

To further evaluate the reversibility of proteinuria, Roels et al. (1997) studied the progression of Cd-induced renal tubular dysfunction in cadmium workers according to the severity of the microproteinuria at the time the exposure was substantially decreased. A total of 32 cadmium male workers were divided into two groups on the basis of historical records of urinary cadmium concentration (CdU) covering the period until 1984. The workers with CdU values of >l0 μg Cd/g creatinine were subdivided further on the basis of the urinary concentration of β_2-microglobulin (β_2-MG-U) measured during the first observation period (1980-1984). In each group, the tubular microproteinuria as reflected by β_2-MG-U and the concentration of retinol-binding protein in urine, as well as the internal cadmium dose as reflected by the concentration of cadmium in blood and urine, were compared between the first and second (1990-1992) observation periods. Increased microproteinuria was often diagnosed in cases with CdU values of >l0 μg Cd/g creatinine. The progression of tubular renal function was found to depend on the extent of the body burden of cadmium (as reflected by CdU) and the severity of the initial microproteinuria at the time high cadmium exposure was reduced or ceased. When cadmium exposure was reduced and β_2-MG-U did not exceed the upper reference limit of 300 μg/g creatinine, the risk of developing tubular dysfunction at a later stage was likely to be low, even in cases with historical CdU values occasionally >l0 but always < 20 μg Cd/g creatinine. When the microproteinuria was mild (β_2-MG-U >300 and ≤1,500 μg/g creatinine) at the time exposure was reduced, and the historical CdU values had never exceeded 20 μg Cd/g creatinine, there was indication of a reversible tubulotoxic effect of cadmium. When severe microproteinuria (β_2-MG-U >1,500 μg/g creatinine) was diagnosed in combination with historical CdU values exceeding 20 μg Cd/g creatinine, cadmium-induced tubular dysfunction was progressive in spite of reduction or cessation of cadmium exposure.

Early animal studies confirmed that renal damage occurs following inhalation exposure to cadmium. Rabbits developed proteinuria after a 4-month inhalation exposure to cadmium metal dust at 4 mg/m^3 for 3 hours per day, 21 days per month; histologic lesions were found after an additional 3-4 months of exposure (Friberg 1950). Friberg (1950) noted that the degree of proteinuria was not especially pronounced. Most subsequent studies using inhalation exposure have not found proteinuria (Glaser et al.

1986; Kutzman et al. 1986; Prigge 1978a, 1978b), primarily because the levels of exposure and durations of follow-up (e.g., l-5 mg/m^3 for intermediate exposures; 0.2-2 mg/m^3 for chronic exposures) that produce serious respiratory effects have not been sufficient to produce a critical concentration of cadmium in the kidney.

Dermal Effects. Dermal toxicity does not appear to be a significant effect of inhalation exposure to cadmium. Studies of workers occupationally exposed to cadmium have not reported dermal effects following acute or chronic exposure (Barnhart and Rosenstock 1984; Bonnell 1955; Friberg 1950). No study was located that specifically examined dermal toxicity in humans or animals following inhalation exposure to cadmium.

Ocular Effects. Ocular toxicity does not appear to be a significant effect of inhalation exposure to cadmium. Studies of workers occupationally exposed to cadmium have not reported ocular effects following acute or chronic exposure (Barnhart and Rosenstock 1984; Bonnell 1955; Friberg 1950). No study was located that specifically examined ocular toxicity in humans following inhalation exposure to cadmium.

Rats exposed to a single 2 hour inhalation exposure to about 100 mg Cd/m^3 as cadmium pigments had excessive lacrimation 4 hours after exposure (Rusch et al. 1986), but this was likely due to a direct irritation of the eyes rather than a systemic effect.

Body Weight Effects. No data were found regarding the effects of inhaled cadmium on human body weights.

In animals, cadmium has been shown to significantly reduce body weights. An acute exposure to cadmium oxide fumes at 112 mg Cd/m^3 for 2 hours (Rusch et al. 1986) and cadmium oxide dust at 4.6 mg Cd/m^3 for 3 hours (Buckley and Bassett 1978b) resulted in a significant reduction of body weight in male rats. Cadmium chloride at 6.5 mg Cd/m^3 for 1 hour or 4.5 mg Cd/m^3 for 2 hours produced significant reductions in male rat body weights (Bus et al. 1978; Grose et al. 1987). Cadmium carbonate at 132 mg Cd/m^3 for 2 hours slowed rat body weight gains (Rusch et al. 1986). NOAELs for acute cadmium chloride exposure have been reported at 0.45 mg Cd/m^3 for 2 hours (Grose et al. 1987); 0.17 mg Cd/m^3 for 10 days, 6 hours a day (Klimisch 1993); and 6 mg Cd/m^3 for 2 hours (Palmer et al. 1986). NOAELs for cadmium sulfide and

cadmium selenium sulfide were much higher at 99 mg Cd/m^3 for 2 hours and 97 mg Cd/m^3 for 2 hours, respectively (Rusch et al. 1986). Levels of cadmium that significantly reduce rat body weights when administered for an intermediate exposure duration have been reported for cadmium chloride at around 1 mg Cd/m^3 for female and male rats (Baranski and Sitarek 1987; Kutzman et al. 1986), for cadmium chloride at around 0.394 mg Cd/m^3 for pregnant female rats (Prigge 1978a), and for cadmium dusts at 0.1 mg Cd/m^3 for female rats (Prigge 1978a). NOAELs have been reported for intermediate exposures to cadmium chloride at 0.394 mg Cd/m^3 for female nonpregnant rats (Prigge 1978a), 0.33 mg Cd/m^3 for rats (Kutzman et al. 1986), and 0.0508 mg Cd/m^3 for male rats (Takenaka et al. 1983). NOVELS have been reported for intermediate exposures to cadmium oxide dust at 0.16 mg Cd/m^3 for female rats (Baranski and Sitarek 1987) and 0.45 mg Cd/m^3 for male rabbits (Grose et al. 1987); and for cadmium sulfide at 1.034 mg Cd/m^3 for male rats (Glaser et al. 1986). A NOAEL for chronic exposure in rats to cadmium sulfate has been reported as 0.95 mg Cd/m^3 (Oldiges and Glaser 1986).

Other Systemic Effects. Yellow discoloration of the teeth has occasionally been reported in workers occupationally exposed to high levels of cadmium (Friberg 1950; Liu et al. 1985). No data were located to indicate that this was related to any functional impairment.

2.2.1.3 Immunological and Lymphoreticular Effects

There is limited evidence for immunological effects following inhalation exposure to cadmium. The blood of workers exposed to cadmium for 1-14 years had a slight but statistically significant decrease in the generation of reactive oxygen species by leukocytes compared to unexposed controls (Guillard and Lauwerys 1989). The toxicological significance of this effect is unclear.

Karakaya et al. (1994) measured blood and urine concentrations of cadmium, and serum IgG, IgM, and IgA in a group of 37 males employed in zinc/cadmium smelters and a small Cd-electroplating plant. Blood cadmium concentrations were significantly higher in exposed workers compared to controls in both the urine (2.39 versus 0.69 μg/l00 mL, $p<0.001$) and the blood (5.55 versus 2.01 μg/g creatinine, $p<0.05$). No differences between the exposed and control serum concentrations of IgG, IgM, and IgA populations were observed. No changes in blood counts of white blood cells (lymphocyte, neutrophil, and eosinophil) were found between exposed and control populations, except for significantly increased monocyte counts.

No other studies were located regarding immunological effects in humans following inhalation exposure to cadmium.

Acute inhalation exposure to cadmium chloride in mice at 0.190 mg Cd/m^3 for 2 hours can affect immune function, causing suppression of the primary humoral immune response (Graham et al. 1978). The NOAEL for immunological effects from the study by Graham et al. (1978) was 0.11 mg Cd/m^3. Krzytyniak et al. (1987) reported spleen lymphocyte cytotoxicity at 0.88 mg Cd/m^3 for 1 hour.

At intermediate-duration exposures, Kutzman et al. (1986) observed increased spleen relative weights and lymphoid hyperplasia from inhalation of cadmium chloride aerosols at 1.06 mg Cd/m^3 6 hours a day, 5 days a week, for 62 days. Prigge (1978b) also observed increased relative spleen weights in pregnant females at 0.394 mg Cd/m^3 for an exposure of 24 hours a day, for 21 days during gestation. Oldiges and Glaser (1986) observed enlarged thoracic lymph nodes in dead animals in a chronic-exposure study with cadmium sulfate at 0.092 mg Cd/m^3 for 22 hours a day, 7 days a week, for 413-455 days; and in an intermediate study with cadmium oxide dust at 0.090 mg Cd/m^3 for 22 hours a day, 7 days a week, for 218 days. However, other studies have found no effect on natural killer cell activity or viral induction of interferon in mice (Daniels et al. 1987). Evidence concerning the effect of inhalation exposure to cadmium on resistance to infection is conflicting, because the same exposure decreases resistance to bacterial infection while increasing resistance to viral infection (Bouley et al. 1982). Representative NOAELs and LOAELs for immunological effects are shown in Table 2-1 and plotted in Figure 2-1.

2.2.1.4 Neurological Effects

Neurotoxicity is not generally associated with inhalation exposure to cadmium, although a few studies have specifically looked for neurological effects. Hart et al. (1989b) reported that in a group of 31 men occupationally exposed to cadmium in a refrigerator coil manufacturing plant (average exposure=14.5 years) there was a modest correlation between cadmium exposure and decreased performance on neuropsychologic tests for attention, psychomotor speed, and memory. The limited number of men studied makes it difficult to evaluate the significance of this effect.

Ijomah et al. (1993) studied an increased prevalence of dementia in elderly people living near an aluminum smelter. Dementia was defined by performance on the Anomalous Sentences Repetition Test (ASRT). Participants were selected among the patients from the general practitioners of the smelter area and the

control area. The study involved two short cognitive tests: a Delayed Recall test and an ASRT. There was no difference in the prevalence of dementia between the smelter group (25 of 168=14.9%) and the reference group (20 of 120=16.7%). There were significant elevations of plasma and red blood cell aluminum and cadmium concentrations. There were also differences in the phospholipid fatty acids of the exposed population (decreased red cell oleic acid and increased linoleic acid), that correlated with the increased aluminum and cadmium red blood cell concentrations.

Rose et al. (1992) studied the presence and severity of olfactory impairment in workers chronically exposed to cadmium fumes generated during a brazing operation. Detailed occupational history, medical history, and smoking history, and symptoms were collected for 55 workers. Body burden was estimated using urinary cadmium levels, and renal damage was assessed by urinary β_2-microglobulin levels. Olfactory test scores from these workers were compared to a reference group of 16 male subjects that were selected according to the following criteria:1) no history of taste or smell complaints, 2) no history of surgery to the upper respiratory tract, 3) no upper respiratory tract infection within 2 days of testing, and 4) no history of having been tested. The dose of the CdO fume received by the workers being evaluated in this study was not reported or estimated. For both the exposed workers and the reference group, 38% were smokers. A significant olfactory impairment was observed in the workers compared to the reference group ($p<0.003$). Thirteen percent of the workers were either moderately or severely hyposmic compared to none in the reference group, 44% of the workers were mildly hyposmic compared to 31% of the reference group, and only 44% of workers were normosmic. Although the odor-identification test findings for workers were similar to those of the reference group, butanol detection threshold scores were significantly lower in the worker population ($p<0.005$). The workers with both higher urinary cadmium levels and tubular proteinuria had the most significant olfactory dysfunction, with a selective defect in odor threshold. The results suggest that chronic occupational cadmium exposure sufficient to cause renal damage is also associated with impairment in olfactory function. Some limitations of the study are that historical exposure to other confounders cannot be ruled out, the classification for nephrotoxicity is based on a single 24-hour urine β_2-microglobulin level, and the smoking history of the reference group was unknown. No other human neurological studies from inhaled cadmium were found.

In rats, cadmium carbonate produced tremors from exposure to 132 mg Cd/m^3 for 2 hours, and cadmium fumes produced reduced activity at 112 mg Cd/m^3 for 2 hours (Rusch et al. 1986). Studies on continuous exposure to cadmium for 30 days have shown no neurological effects at 0.105 mg Cd/m^3 for cadmium chloride, 0.098 mg Cd/m^3 for cadmium dusts, or 1.034 mg Cd/m^3 for cadmium sulfide (Glaser et al. 1986).

Cadmium chloride had no neurological effects at 0.33 mg Cd/m^3 for 5 days a week, 6 hours a day, for a total of 62 daily exposures, but did significantly increase relative brain weight at 1.034 mg Cd/m^3 (Kutzman et al. 1986). No other studies were located regarding neurological effects in adult animals after inhalation exposure to cadmium. Neurological effects in offspring of rats exposed to cadmium by inhalation during gestation are discussed in Section 2.2.1.5. NOAELs and LOAELs from the above studies are listed in Table 2-1 and plotted in Figure 2-1.

2.2.1.5 Reproductive Effects

Evidence is insufficient to determine an association between inhalation exposure to cadmium and reproductive effects.

Gennart et al. (1992) studied male reproductive effects of cadmium in 83 occupationally exposed bluecollar Belgian workers in 2 smelting operations. The workers were exposed to cadmium in dust and fumes. Information was recorded on age, residence, education, occupational and health history, actual and previous occupations, smoking habits, and coffee and alcohol consumption. Fertility parameters included dates of birth of wife and husband, date of marriage, and the number of children born alive and their dates of birth. Blood and urine samples were also collected from each worker. Some cadmium workers had been excessively exposed; 25% of them already had signs of kidney dysfunction as evidenced by microproteinuria and/or a serum creatinine level above 13 mg/L. No effects were observed on male fertility as evidenced by no significant influence of cadmium on the probability of a live birth. The limitation of this study, as described by the authors, included the fact that the wives were not interviewed and, therefore, factors that could have influenced their reproductive ability were not considered.

Men occupationally exposed to cadmium at levels causing renal damage had no change in testicular endocrine function, as measured by serum levels of testosterone, luteinizing hormone, and follicle stimulating hormone (Mason 1990). Noack-Fuller et al. (1992) measured concentrations of cadmium, lead, selenium, and zinc in whole semen and seminal fluid of 22 unexposed men (13 were smokers) to evaluate intra-individual variability and to examine the statistical association between element concentrations and semen characteristics and sperm motion parameters. None of the men had any known occupational exposure to cadmium.

Concentrations of cadmium were similar in semen and seminal plasma (0.40±0.23 and 0.34±0.19 μg/L, respectively). Sperm motility ($p<0.02$), linear velocity ($p<0.001$), and curvilinear velocity (CV) ($p<0.002$) were significantly correlated with semen cadmium levels. Intra-individual coefficients of variation for sperm count (CV=46±4%) and sperm concentration (CV=37±6%) showed the highest variability. No positive correlation was found between cadmium concentration in semen and sperm density. The smokers had slightly elevated levels of cadmium. The concentrations of cadmium in semen of these volunteers was very low. Additional studies are needed (preferably with larger sample sizes) to evaluate the robustness of this association between cadmium (at the low levels detected) and sperm motion parameters. Saaranen et al. (1989) measured cadmium, selenium, and zinc in seminal fluid and serum in 64 men, half of whom were smokers. Smokers had significantly higher serum cadmium concentration than nonsmokers. Seminal fluid cadmium was also elevated in smokers, and was higher than serum cadmium in smokers consuming more than 20 cigarettes daily. Semen quality was measured for volume, sperm density, morphology, motility, and number of immature germ cells. No differences were found in semen quality or fertility between smokers and nonsmokers. There was no significant correlation between seminal fluid cadmium levels and semen quality or fertility.

Xu et al. (1993a) measured trace elements in blood and seminal plasma and their relationship to sperm quality in 221 Singapore men (age range 24-54; mean 34.8) who were undergoing initial screening for infertility. Men with significant past medical history and those who had been occupationally exposed were excluded. Parameters monitored included semen volume and sperm density, motility, morphology, and viability. Graphite furnace atomic absorption was used to determine cadmium concentration in blood and semen. No differences were observed in sperm quality (density, motility, morphology, volume, and viability) of the 221 men compared to a cohort of 38 fertility proven men (wives had recently conceived). Cadmium levels in blood did have a significant inverse relationship with sperm density ($r=-0.15$, $p<0.05$) in oligospermic men (sperm density below 20 million/ml), but not in normospermic men. There was a significant reduction in sperm count in men with blood cadmium of >1.5 μg/L. Also, there was a weak negative correlation between defective sperm and concentration of cadmium in semen ($r=-0.21$, $p<0.05$). The volume of semen was inversely proportional to the cadmium concentration in semen ($r=-0.29$, $p<0.05$). These findings suggest that cadmium may have an effect on the male reproductive system. Limitations of the study include lack of control for potential confounding factors such as the lower levels of zinc in seminal plasma, and the validity of using infertile men as the study group (i.e., again because of confounding factors that may be affecting both cadmium levels and sperm levels).

A post-mortem study of men occupationally exposed to cadmium who died from emphysema found high levels of cadmium in their testes, but no histologic lesions other than those attributable to terminal illness (Smith et al. 1960)

Russian women occupationally exposed to cadmium concentrations up to 35 mg/m^3 had no irregularities in their menstrual cycles (Tsvetkova 1970). Fertility and other indices of reproductive function were not measured. No studies were located that showed reproductive effects in women following inhalation exposure to cadmium.

In rats, exposure to cadmium oxide dusts at 1 mg Cd/m^3 for 5 hours a day, 5 days a week, for 20 weeks, increased the duration of the estrous cycle (Baranski and Sitarek 1987). Male and female rats exposed to cadmium concentrations of 1 mg/m^3 for 6 hours a day, 5 days a week, for 62 days and subsequently mated with unexposed controls showed no loss in reproductive success measured by viable embryos and preimplantation losses, but males did have an increased relative testes weight (Kutzman et al. 1986). Tsvetkova (1970) studied rats exposed to cadmium sulfate aerosols at 2.8 mg Cd/m^3 before and during pregnancy. A lengthening of the estrous cycle was observed 2 months after the start of exposure in onehalf of the exposed animals. By the fourth month, diestrus was 6.2 days in the exposed group compared to 1.2 days in controls. No other studies were found on reproductive effects in animals. NOAELs and LOAELs from the above studies are listed in Table 2-1 and plotted in Figure 2-l.

2.2.1.6 Developmental Effects

Russian women occupationally exposed to cadmium at concentrations ranging from 0.02 to 35 mg/m^3 had offspring with decreased birth weights compared to unexposed controls, but without congenital malformations (Tsvetkova 1970). No association was found between birth weights of offspring and length of maternal cadmium exposure. Moreover, no control was made for parity, maternal weight, gestational age, or other factors known to influence birth weight (Tsvetkova 1970). A nonsignificant decrease in birth weight was found in offspring of women with some occupational exposure to cadmium in France; however, no adverse effects were documented in these newborns (Hue1 et al. 1984). Hue1 et al. (1984) used hair samples to estimate exposure, and this method is limited without controls to distinguish between exogenous and endogenous sources. No other studies were located regarding developmental effects in humans after inhalation exposure to cadmium.

Developmental toxicity in offspring of female rats exposed to cadmium oxide at 0.02 mg Cd/m^3 for 5 hours a day, 5 days a week, for 4-5 months prior to mating and during the first 20 days of gestation was manifest by delayed ossification, decreased locomotor activity, and impaired reflexes in offspring (Baranski 1985). Decreases in weight gain, osteogenesis, and viability were also noted at concentrations of 0.16 mg/m^3 (Baranski 1985). Maternal weight gain and fetal weight were reduced in pregnant rats exposed to cadmium chloride aerosols during gestation at concentrations of 0.204, 0.394, or 0.581 mg/m^3 (Prigge 1978b). The decrease in fetal weight was statistically significant only at 0.581 mg/m^3 (Prigge 1978b). LOAELs from these studies are listed in Table 2-1 and plotted in Figure 2-1.

2.2.1.7 Genotoxic Effects

Examination of lymphocytes from workers occupationally exposed to both cadmium and. lead have shown statistically significant increases in chromosomal aberrations (Bauchinger et al. 1976; Deknudt and Leonard 1975; Deknudt et al. 1973), but not in men exposed primarily to cadmium (Bui et al. 1975; O'Riordan et al. 1978).

No studies were located regarding genotoxic effects in animals after inhalation exposure to cadmium. Other genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

The relationship between occupational exposure to cadmium and increased risk of cancer (particularly lung and prostate cancer) has been explored in a number of epidemiologic studies. The data and some of the analyses for lung cancer are conflicting, and controls for confounding factors such as co-exposure with other metal carcinogens and smoking have occurred in only a few of the studies. Overall, the results provide little evidence of an increased risk of lung cancer in humans following prolonged inhalation exposure to cadmium. Initial studies indicated an elevation in prostate cancer among men occupationally exposed to cadmium (Kipling and Waterhouse 1967; Kjellstrom et al. 1979; Lemen et al. 1976), but subsequent investigations found either no increases in prostate cancer or increases that were not statistically significant (Elinder et al. 1985c; Kazantzis et al. 1988; Sorahan 1987; Thun et al. 1985). Based on an analysis of the mortality data from a 5-year update of the cohort from 17 plants in England and a review of

the other epidemiological evidence, Kazantzis et al. (1992) concluded that cadmium does not appear to act as a prostatic carcinogen.

Evaluations of occupationally exposed cohorts in countries other than the United States have found some increases in lung cancer, but no clear relationship between level and duration of cadmium exposure and increased risk of lung cancer. Cigarette smoking was also a confounding factor. These cohorts came from an English zinc-lead-cadmium smelter (Ades and Kazantzis 1988), from 17 different manufacturing or processing facilities involving cadmium in England (Kazantzis et al. 1988), from a nickel-cadmium battery plant in Sweden (Elinder et al. 1985c), and from a nickel-cadmium battery plant in England (Sorahan 1987). The most recent report comes from Sorahan et al. (1995) on mortality rates (lung cancer and nonmalignant respiratory diseases) in 347 copper cadmium alloy workers in the United Kingdom. The authors state that the study results are consistent with the hypothesis that exposure to cadmium oxide fumes increases the risk of mortality from chronic non-malignant diseases of the respiratory system, but do not support the hypothesis that exposure increases the risks of mortality for lung cancer.

An increased risk of lung cancer from cadmium exposure was reported in studies on the only U.S. cohort (workers in a cadmium recovery plant in Globe, Colorado) (Thun et al. 1985; Stayner et al. 1992), but subsequent studies have attributed the increase to either arsenic exposure and/or smoking (Lamm et al. 1992, 1994; Sorahan et al. 1997). These studies and the conflicting results are discussed in detail below.

A statistically significant, 2-8-fold excess risk of lung cancer was reported in the highest exposure group (cumulative exposures >8 years x mg/m^3), and the dose-response trend over the three exposure groups was highly significant (Thun et al. 1985). Confounding factors included possible exposure to the heavy metals, arsenic (Thun et al. 1989; Kazantzis et al. 1992) and nickel (Sorahan 1987), which are known human lung carcinogens. The data in the U.S. cohort supported an analysis that controlled for the effects of smoking.

Stayner et al. (1992) used data from a retrospective study on lung cancer mortality in the United States to further evaluate the lung cancer risk associated with cadmium exposure in the U.S. cohort. The analysis controlled for smoking and for ethnicity (i.e., Hispanic and non-Hispanic workers). Lung cancer mortality rates are lower for Hispanics compared to non-Hispanics. The cohort included 606 male Hispanic and non--Hispanic workers with 16,898 person-years of combined work history. Medical records were use to examine death rates and occurrences of lung cancer which were then compared with length of exposure and exposure dose of cadmium. Vital status was successfully determined for approximately 98% of this

of cadmium. Vital status was successfully determined for approximately 98% of this cohort. A total of 162 deaths were identified, including eight additional lung cancers through December 31, 1984, that were not included in the Thun et al. (1985) analysis. Workers were sorted into 4 groups by cumulative exposure (<584, 585-1,460, 1,461-2,920, and >2,921 mg-days/m^3) and by number of years since the first exposure (<10, 10-19, >20 years). The findings were analyzed using a modified life-table analysis to estimate standardized mortality ratios (SMR), and various functional forms (i.e., exponential, power, additive relative rate, and linear) of the Poisson and Cox proportional hazards models to examine the dose-response relationship. Estimates of working lifetime risks (45 years) were developed using an approach that corrects for competing causes of death. The mortality rate for white U.S. males was used in this analysis as the referent rate for both the Hispanic and non-Hispanic workers. Lung cancer mortality was significantly elevated among non-Hispanics and less than expected among Hispanics (as would be predicted from the use of the white male referent rate). The lung cancer SMR increased with cumulative cadmium exposure and was nearly significant for the entire cohort (SMR=149, 95% CI=95, 222; p=0.076, two-tails). The SMR was significantly elevated in the highest exposure group (>2,921 mg-days/m^3) for the combined cohort (SMR=272,95% CI=123,513), and for the three highest exposure groups for the non-Hispanic groups. A significant excess of lung cancer mortality was also observed among workers in the longest time-since-firstexposure category (>20 years) for the combined cohort (SMR=161, 95 % CI= 100, 248) and for non-Hispanics (SMR=233, 95% CI=141, 365). A statistically significant dose-response relationship was evident in nearly all of the regression models evaluated. Based on this analysis, the lifetime excess of lung cancer at the previous OSHA standard for cadmium fume of 100 μg/m^3 would be approximately 50-l 1 lung cancer deaths per 1,000 workers exposed to cadmium for a working lifetime (45 years). At the current OSHA standard of 5 μg/m^3 (OSHA 1992), the lifetime risk of lung cancer was predicted to be approximately 2.6-6 lung cancer deaths per 1,000 workers exposed to cadmium for 45 years (Stayner et al. 1992).

Stayner et al. (1992) also performed an indirect assessment of confounding effects of exposure to arsenic. No direct arsenic exposure data were available, so an indirect assessment consisted of a comparison of SMRs for populations employed before and after 1940, a date prior to which arsenic exposure was reportedly high (i.e., the plant was an arsenic smelter prior to 1926). The authors propose that the levels of arsenic declined substantially after 1940. Among non-Hispanics hired before 1940, a clear dose-response trend was evident, and a significantly elevated SMR (SMR=381, 95% CI=l00248) was observed within the highest exposure group (>2,921 mg-days/m^3). For those non-Hispanic individuals hired during or after 1940, a significantly elevated SMR was observed among workers in the 585-1,460 mg-days/m^3

(SMR=281) and 1,461-2,920 mg-days/m^3 (SMR=470) exposure groups. This analysis indicates that there was no significant effect on lung cancer mortality from cumulative cadmium exposure because of year of hire; in fact, the authors report that their dose-response analysis demonstrated a greater dose-response relationship for workers hired after 1939.

Lamm et al. (1992, 1994) used nearly the same data set for the U.S. cohort as Stayner et al. (1992) in a nested case-control analysis that used the period of hire as a surrogate for arsenic exposure. Based on this analysis as a means to control for the confounding factor of arsenic exposure, Lamm et al. (1992, 1994) reported no residual association of lung cancer with cadmium in the Globe, Colorado, cohort. They also reported that cases were more than eight times more likely to have been cigarette smokers than were controls. Lamm et al. (1992, 1994) conclude that arsenic exposure and cigarette smoking were the major determinants of lung cancer risk, not cadmium exposure.

The reasons for these conflicting conclusions based on the same cohort data are unclear. Doll (1992) suggested some possible reasons including: (1) that the total number of cases was small (n=25) and that only 21 of these cases were included in both studies (i.e., each study included some cases that were not included in the other study); (2) that Stayner et al. (1992) used national rather than regional mortality rates; (3) that the Lamm et al. (1992, 1994) control series was overmatched, although the matching by date of hire was necessary to control for arsenic exposure; and (4) that there are some concerns about the validity (i.e., biologica1 relevance) of the dose-response-models used by Stayner et al. (1992). In a response to Doll (1992), Stayner et al. (1993) reported that use of regional mortality rates would increase rather than decrease support for their conclusion, and that the nested case-control analysis of Lamm et al. (1992) used overmatched controls. Stayner et al. (1993) provided additional analyses including the use of the Arrnitage-Doll multistage model to support the conclusion of an increased risk of cancer from cadmium exposure.

Sorahan and Lancashire (1994) subsequently raised concerns about inconsistencies and inaccuracies in the NIOSH job history data used in these studies on the U.S. cohort. Sorahan and Lancashire (1997) then conducted further analyses, based on detailed job histories extracted from time sheet records, to better resolve the potential confounding affects of arsenic. Poisson regression was used to investigate risks of mortality from lung cancer in relation to four concentrations of accumulative exposure to cadmium (<400, 400-999, 1000-1999, and >2000 mg-days/m^3). After adjustment for age attained, year of hire, and Hispanic ethnicity; Sorahan and Lancashire (1997) report a significant positive trend ($p<0.05$) between

cumulative exposure to cadmium and risks of mortality from lung cancer. However, when the exposure to cadmium was evaluated with or without concurrent exposure to arsenic, a significant trend for lung cancer was only found for exposure to cadmium received in the presence of arsenic trioxide. Since there were only 21 deaths from lung cancer, Sorahan and Lancashire (1997) state that it is impossible to determine which of the following three hypotheses is the correct one: (1) cadmium oxide in the presence of arsenic trioxide is a human lung carcinogen, (2) cadmium oxide and arsenic trioxide are human lung carcinogens and cadmium sulphate and cadmium sulphide are not (i.e., cadmium sulphate and cadmium sulphide were the main cadmium compounds of exposure when arsenic was not present), or (3) arsenic trioxide is a human carcinogen and the three cadmium compounds are not carcinogenic.

Studies in rats provide strong evidence of the lung carcinogenic potential of chronically inhaled cadmium. Oldiges et al. (1989) reported a clear dose response increase in lung tumors in male and female rats from an 18-month continuous exposure to either cadmium chloride, cadmium oxide dusts, cadmium oxide fume, cadmium sulfate, or cadmium sulfide. In the cadmium chloride study at 30 $\mu g/m^3$, the observation period in the males had to be shortened to 30 months (rather than 31) because of mortality in excess of 75%. No lung tumors were observed in control rats after 31 months of observation. A high incidence of nodules and tumors was seen in 30 $\mu g/m^3$ exposures to $CdCl_2$ in both males and females. Results showed lung nodules in 18 of 20 males and 15 of 18 females and primary lung tumors in 15 of 20 males and 13 of 18 females. Tumor incidence as bronchioalveolar adenomas, adenocarcinomas, squamous cell carcinomas, or combined were 2, 12, 0, and 1 for males; and 4, 7, 0, and 2 for females, respectively. Increased lung tumors in males and females were also observed with chronic exposures to cadmium oxide dust or fume at 30 $\mu g/m^3$, to cadmium sulfate at 90 $\mu g/m^3$, and to cadmium sulfide at 90 $\mu g/m^3$ (Oldiges et al. 1989). Cadmium sulfate produced by photolysis of cadmium sulfide under the experimental conditions may have contributed to some of the response observed with cadmium sulfide (Konig et al. 1992).

Takenaka et al. (1983) also demonstrated cadmium carcinogenicity in male rats exposed to cadmium chloride aerosols at 0.0134, 0.0257, and 0.0508 mg Cd/m^3 for 18 months. The exposure produced a dose related increase in lung epidermoid carcinomas, adenocarcinomas, and mucoepidermoid carcinomas starting at 20 months. No other type of tumor was observed to increase with increasing dose.

In a protocol similar to the studies by Oldiges et al. (1989), Heinrich et al. (1989) did not observe an increase in lung tumors in male or female Syrian golden hamsters from chronic inhalation exposure to either CdO dust or fumes, $CdCl_2$, $CdSO_4$, or CdS. In female mice, lung tumor incidence increased at all

dose levels, but incidence in the controls was also high, and the cadmium-induced increases were not statistically significant. Lung tumors in the cadmium-treated mice also did not increase in a dose responsive manner except for a weak increase from exposure to the cadmium oxide fumes (Heinrich et al. 1989).

The Environmental Protection Agency (EPA) has classified cadmium as a probable human carcinogen by inhalation (Group Bl), based on limited evidence of an increase in lung cancer in humans (Thun et al. 1985) and sufficient evidence of lung cancer in rats (IRIS 1996; Takenaka et al. 1983). EPA has calculated an inhalation unit risk (the risk corresponding to lifetime exposure to 1 $\mu g/m^3$) of $1.8x10^{-3}$ (IRIS 1996). A range of concentrations that correspond to upper bound lifetime excess risks of 10^{-4} to 10^{-7} is shown in Figure 2-1. The National Toxicology Program (NTP) has classified cadmium and certain cadmium compounds as substances that are reasonably anticipated to be carcinogens, based on limited evidence for carcinogenicity from studies in humans and sufficient evidence for carcinogenicity in humans (NTP 1994). In contrast, the International Agency for Research for Research on Cancer (IARC) has classified cadmium as carcinogenic to humans (Group l), based on sufficient evidence for carcinogenicity in both human and animal studies (IARC 1993). The differences in conclusions about the adequacy of the human carcinogenicity data are further discussed in Section 2.5, Relevance to Public Health.

2.2.2 Oral Exposure

Information on health effects of oral exposure to cadmium in humans is derived mainly from studies of residents living in cadmium-polluted areas. Cadmium exposure in these populations is often estimated by blood or urinary cadmium levels (see Section 2.7.1). Exposure in these cases occurs primarily through the diet, but smokers in these cohorts are also exposed to cadmium by inhalation. Smoking, however, is treated as a confounding variable, not as an exposure route because of the large number of toxic compounds (in addition to cadmium) present in cigarette smoke, and because the primary concern is effects attributable to cadmium. Cadmium is more readily found in the free ionic form in water; while in food, the cadmium ion generally exists in a complex with a variety of ligands, including proteins such as metallothionein (Crews et al. 1989; Groten et al. 1990; Nordberg et al. 1986). Experimental studies in animals have generally used soluble salts of cadmium (such as cadmium chloride) for food, drinking water, and gavage exposures. The toxicological properties of the cadmium ion do not appear to depend on the counter ion, although absorption may be significantly affected by protein complexes (see Section 2.3.1.2).

2.2.2.1 Death

Intentional ingestion of cadmium has been used as a means of suicide, causing death due to massive fluid loss, edema, and widespread organ destruction (Buckler et al. 1985; Wisniewska-Knypl et al. 1971). The doses ingested in two known fatal cases were estimated to be 25 mg Cd/kg from cadmium iodide (Wisniewska-Knypl et al. 1971) and 1,840 mg Cd/kg from cadmium chloride (Buckler et al. 1986). Time to death after cadmium iodide ingestion was 7 days (Wisniewska-Knypl et al. 1971) and 33 hours after ingestion of the cadmium chloride (Buckler et al. 1986).

In rats and mice, acute oral LD_{50} (lethal dose, 50% kill) values for cadmium range from about 100 to 300 mg/kg (Baer and Benson 1987; Basinger et al. 1988; Kostial et al. 1978; Kotsonis and Klaassen 1978; Shimizu and Morita 1990). The lowest dose causing death (2 of 20 animals) was 15.3 mg/kg in Sprague-Dawley rats (Borzelleca et al. 1989). Very young animals have lower LD_{50} values than adult animals (Kostial et al. 1978, 1989a); this effect may be related to the greater fractional absorption of ingested cadmium in the immature organism (see Section 2.3.1.2).

Deaths related to cadmium exposure have been reported in only two of the intermediate exposure studies found. In a study in Wistar rats exposed to cadmium chloride by gavage at 40 mg Cd/kg daily, 5 days a week, for up to 14 weeks; 4 of 13 female Wistar rats died by 8 weeks (Baranski and Sitarek 1987). In mice, Blakley (1986) studied the effect of cadmium on chemical- and viral-induced tumor production. Female albino Swiss mice (8 weeks old, N=41) were administered $CdCl_2$ in the drinking water for 280 days at doses of 0, 5, 10, or 50 ppm. These mice have a high incidence of spontaneous lymphocytic leukemia of thymic origin. A significant 33% increase ($p=0.0228$, chi-square analysis) in deaths from virally induced leukemia was observed from exposure to 1.9 or 9.5 mg Cd/kg/day. The deaths were attributed to cadmium-impaired immunosurveillance mechanisms that control expression of the murine lymphocytic leukemia virus.

Representative LOAEL values for lethality after acute oral exposure to cadmium are recorded in Table 2-2 and plotted in Figure 2-2.

Table 2-2. Levels of Significant Exposure to Cadmium - 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	Human	once (IN)				1840 F (fatal human dose within 1-2 days)	Buckler et al. 1986 $CdCl_2$
2	Human	once (IN)				25 M (fatal human dose within 7 days)	Wisniewska-Knypl et al. 1971 CdI2
3	Rat (Sprague-Dawley)	10 d 1 x/d (GW)				15.3 (2/10 males, 1/10 females died)	Borzelleca et al. 1989 $CdCl_2$
4	Rat (Sprague-Dawley)	once (GW)				15.3 (1/10 males, 1/10 females died)	Borzelleca et al. 1989 $CdCl_2$
5	Rat (NS)	once (G)				29 (LD_{50} at 8 days; 2 wk old)	Kostial et al. 1978 $CdCl_2$
						129 F (LD_{50} at 8 days; 6 wk old)	
						104 F (LD_{50} at 8 days; 18 wk old)	
6	Rat (Sprague-Dawley)	once (GW)				225 M (LD_{50} at 14 days)	Kotsonis and Klaassen 1977 $CdCl_2$
7	Rat (Sprague-Dawley)	2 wk (W)				42 M (7/9 died within 2 weeks)	Kotsonis and Klaassen 1978 $CdCl_2$
8	Rat (Sprague-Dawley)	once (GW)				327 M (LD_{50} at 24 hours; fed rats)	Shimizu and Morita 1990 $CdCl_2$
						107 M (LD_{50} at 24 hours; fasted rats)	

Table 2-2. Levels of Significant Exposure to Cadmium - 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
9	Mouse (CBA/Bom)	once (GW)				30.4 M (2/54 died within 10 days)	Andersen et al. 1988 $CdCl_2$
10	Mouse (Swiss-Webster)	once (GW)				95.5 M (LD_{50} at 96 hours)	Baer and Benson 1987 $CdCl_2$
11	Mouse (ICR)	once (GW)				112 M (5/10 died within 8 days)	Basinger et al. 1988 $CdCl_2$
	Systemic						
12	Human	once (IN)	Cardio			25 M (rhythmic disturbance, ventricular fibrillation)	Wisniewska-Knypl et al. 1971 $CdCl_2$
			Gastro			25 M (hemorrhagic gastroenteritis)	
			Renal			25 M (hypoalbuminemia, anuria)	
			Metab		25M (metabolic acidosis, hyperthermia)		
13	Rat (Wistar)	10 d Gd 7-16 once (GW)	Bd Wt	2 F	12 F (14% decreased maternal body weight)		Baranski 1985 $CdCl_2$

Table 2-2. Levels of Significant Exposure to Cadmium - 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
14	Rat (Sprague-Dawley)	10 d 1 x/d (GW)	Hemato	31.3 M	65.6 M (increased hemoglobin, hematocrit, erythrocytes)		Borzelleca et al. 1989 $CdCl_2$
				138 F			
			Hepatic	65.6 M		138 M (focal necrosis of hepatocytes)	
			Renal			15.3 (focal necrosis of tubular epithelium)	
			Bd Wt		15.3 M (18% decreased body weight)	31.3 M (23% decreased body weight)	
				31.3 F	65.6 F (18% decreased body weight)		
15	Rat (Sprague-Dawley)	10 d (W)	Hepatic	13.9			Borzelleca et al. 1989 $CdCl_2$
			Renal	13.9			
			Bd Wt	13.9			
				1.1 M	7.8 M (14% decreased body weight)	11.2 M (25% decreased body weight)	
16	Rat (Sprague-Dawley)	once (GW)	Cardio	150 M			Kotsonis and Klaassen 1977 $CdCl_2$
			Hemato	150 M			
			Hepatic	150 M			
			Renal		25 M (50% decrease in urine flow for first 2 days)		
			Bd Wt	100	150 M (initial 12% decreased body weight)		

Table 2-2. Levels of Significant Exposure to Cadmium - 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
17	Rat (Long- Evans)	10 d 1 x/d Gd 6-15 (GW)	Gastro	6.13 F		61.32 F (intestinal necrosis, hemorrhage, ulcers)	Machemer and Lorke 1981 $CdCl_2$
			Bd Wt	1.84 F	6.13 F (transient 27% decrease in body weight gain during treatment)	18.39 F (persistent 50% decrease in maternal body weight gain)	
18	Rat (Long- Evans)	10 d Gd 6-15 (F)	Gastro	12.5 F			Machemer and Lorke 1981 $CdCl_2$
			Bd Wt	3.5 F	12.5 F (transient 19% decrease in maternal body weight gain during treatment)		
19	Rat (Wistar)	12 d (W)	Hemato			12 M (anemia)	Sakata et al. 1988 $CdCl_2$
20	Rat (Sprague-Dawley)	once (GW)	Hepatic		75M (focal degeneration and necrosis of parenchymal cells)		Shimizu and Morita 1990 $CdCl_2$
21	Mouse (CBA/Bom)	once (GW)	Gastro	15.7 M	30.4 M (gastritis and enteritis)	88.8 M (severe gastric necrosis)	Andersen et al. 1988 $CdCl_2$
			Hepatic	15.7 M	30.4 M (fatty infiltration of liver cells, occasional hepatocellular necrosis)		
			Renal	59.6		88.8 M (tubular necrosis and casts)	
22	Mouse (ICR)	once (GW)	Gastro			112 M (glandular stomach epithelial necrosis)	Basinger et al. 1988 $CdCl_2$
			Hepatic			112 M (extensive hepatocellular coagulative necrosis)	
			Renal	112 M			

Table 2-2. Levels of Significant Exposure to Cadmium - 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
	Immunological/Lymphoreticular						
23	Rat (Sprague-Dawley)	10 d 1 x/d (GW)		31.3 F 65.6 M	65.6 F (increased leukocyte counts)		Borzelleca et al. 1989 $CdCl_2$
	Neurological						
24	Rat (Sprague-Dawley)	once (GW)		25 M	50M (decreased motor activity)		Kotsonis and Klaassen 1977 $CdCl_2$
	Reproductive						
25	Rat (Wistar)	once (GW)		50 M		100 M (testicular necrosis)	Bomhard et al. 1987 $CdCl_2$
26	Rat (Sprague-Dawley)	10 d 1 x/d (GW)		138 F		65.6 M (testicular atrophy and loss of spermatogenic elements)	Borzelleca et al. 1989 $CdCl_2$
27	Rat (Sprague-Dawley)	once (GW)		25 M			Dixon et al. 1976 $CdCl_2$
28	Rat (Sprague-Dawley)	once (GW)		50 M		100 M (testicular necrosis; decr. spermatogenesis; decr. # females producing pups)	Kotsonis and Klaassen 1977 $CdCl_2$
29	Rat (Long- Evans)	10 d 1 x/d Gd 6-15 (GW)		18.39 F		61.32 F (decreased percent fertilized and percent pregnant)	Machemer and Lorke 1981 $CdCl_2$

Table 2-2. Levels of Significant Exposure to Cadmium - 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
30	Rat (Long- Evans)	10 d 1 x/d Gd 6-15 (F)		12.5 F			Machemer and Lorke 1981 $CdCl_2$
31	Mouse (CBM/ Bom)	once (GW)		30.3 M		59.6 M (testicular necrosis)	Andersen et al. 1988 $CdCl_2$
	Developmental						
32	Rat (Wistar)	10 d Gd 7-16 once (GW)			2 F (delayed ossification of the sternum and ribs)	40 (fused lower limbs, absent limbs, decreased number of live fetuses, increased number of resorptions)	Baranski 1985 $CdCl_2$
33	Rat (Long- Evans)	10 d 1 x/d Gd 6-15 (GW)		6.13		18.39 (malformations including dysplasia of facial bones and rear limbs, edema, exenteration, cryptorchism, and palatoschisis)	Machemer and Lorke 1981 $CdCl_2$
34	Rat (Long- Evans)	10 d Gd 6-15 (F)		12.5			Machemer and Lorke 1981 $CdCl_2$
	INTERMEDIATE EXPOSURE						
	Death						
35	Rat (Wistar)	14 wk 5 d/wk (GW)				40 F (4/13 died by week 8; 7/13 by week 14)	Baranski and Sitarek 1987 $CdCl_2$
36	Mouse (Swiss)	280 d (W)				1.9 F (24/41 died by 280 days)	Blakley 1986 $CdCl_2$

Table 2-2. Levels of Significant Exposure to Cadmium - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL				Reference Chemical Form
					Less Serious (mg/kg/day)		Serious (mg/kg/day)		
	Systemic								
37	Monkey (Rhesus)	10 wk (F)	Bd Wt	5 M					Chopra et al. 1984 $CdCl_2$
38	Rat (Wistar)	21 d Gd 1-20 (W)	Bd Wt		9.6	(37% decreased maternal weight gain)			Baranski 1987 $CdCl_2$
			Other		9.6	(decreased water [18%] and food [30%] intake)			
39	Rat (Wistar)	14 wk 5 d/wk (GW)	Bd Wt	4 F			40 F	(29% decreased maternal body weight)	Baranski and Sitarek 1987 $CdCl_2$
40	Rat (Sprague-Dawley)	2-10 mo (W)	Renal				30 F	(B_2-microglobulinuria)	Bernard et al. 1988a $CdCl_2$
41	Rat (Sprague-Dawley)	4 or 7 mo (W)	Renal				15.2 F	(albuminuria, transferrinuria, B_2-microglobulinuria)	Cardenas et al. 1992a $CdCl_2$
42	Rat (Sprague-Dawley)	190 d (W)	Cardio		1.4 M	(20% increase in diastolic blood pressure)			Carmignanti and Boscolo 1984 Cd acetate
			Bd Wt	2.8 M					

Table 2-2. Levels of Significant Exposure to Cadmium - Oral (continued)

Key to[a] figure	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
43	Rat (Sprague-Dawley)	12 wk (W)	Hepatic			8.58 (hepatic necrosis of central lobules)	Cha 1987 $CdCl_2$
			Renal			8.58 M (necrosis of proximal tubular epithelial cells and cloudy swelling)	
			Bd Wt		8.58 M (23% decreased in body weight gain; 9% total body weight decrease)		
44	Rat (Wistar)	170 d (W)	Bd Wt	56 F			Cifone et al. 1989a $CdCl_2$
45	Rat (Sprague-Dawley)	3 mo (W)	Hemato			2.0 (anemia)	Decker et al. 1958 $CdCl_2$
			Bd Wt		2.0 F (15% decreased body weight)	2.0 M (25% decreased body weight)	
46	Rat (Wistar)	4-60 wk (W)	Renal		1.18 (vesiculation of proximal tubules)		Gatta et al. 1989 $CdCl_2$
47	Rat (Wistar)	15 d 1 x/d (GW)	Hepatic		10M (increased lipid peroxidation)		Gill et al. 1989b $CdCl_2$
			Renal		10M (increased lipid peroxidation)		
			Bd Wt	10			
48	Rat	4 wk (F)	Hemato			2.5 M (anemia)	Groten et al. 1990 $CdCl_2$
			Hepatic		2.5 M (increased ALT and AST activities)		
			Renal	2.5 M			

Table 2-2. Levels of Significant Exposure to Cadmium - 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
49	Rat (Wistar)	120 d (W)	Hemato			3.6 M (anemia)	Itokawa et al. 1974 $CdCl_2$
			Musc/skel			3.8 M (osteomalacia in Ca deficient animals)	
			Renal			3.6 M (tubular necrosis and casts, glomerular adhesions)	
50	Rat (Sprague-Dawley)	7 wk (F)	Cardio			2.5 M (congested myocardium, separation of muscle fibers)	Jamall et al. 1989 $CdCl_2$
			Renal	2.5 M			
			Bd Wt	2.5 M			
51	Rat (Wistar)	90 d (W)	Hemato			8 F (anemia)	Kawamura et al. 1978 $CdCl_2$
			Musc/skel			8 F (osteomalacia changes)	
			Renal			8 F (decreased renal clearance)	
			Endocr	8 F			
			Bd Wt		8 F (12% decreased body weight)		
52	Rat (Sprague-Dawley)	22 days Gd 0-21 (W)	Hemato		1.5 F (slight anemia)		Kelman et al. 1978 form not specified
			Musc/skel	3.8 F			
53	Rat (albino)	10 wk (W)	Bd Wt	4.8			Kostial et al. 1993 $CdCl_2$

Table 2-2. Levels of Significant Exposure to Cadmium - 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
54	Rat (Sprague-Dawley)	24 wk (W)	Resp	8.0 M			Kotsonis and Klaassen 1978 $CdCl_2$
			Cardio	8.0 M			
			Gastro	8.0 M			
			Hemato	8.0 M			
			Musc/skel	8.0 M			
			Hepatic	8.0 M			
			Renal	1.2 M		3.1 M (proteinuria, slight focal tubular necrosis)	
			Endocr	8.0 M			
			Bd Wt	8.0 M			
55	Rat	1 or 2 mo (W)	Musc/skel			3.8 F (reduced bone accretion; osteoporosis in Ca deficient rats)	Larsson and Piscator 1971 form not specified
56	Rat (Wistar)	3 mo (F)	Cardio	3.0			Loeser and Lorke 1977a $CdCl_2$
			Hemato	3.0			
			Hepatic	3.0			
			Renal	3.0			
			Endocr	3.0			
			Bd Wt	3.0			
57	Rat (Sprague-Dawley)	6-16 wk (W)	Resp			2.4 (lung fibrosis)	Miller et al. 1974b $CdCl_2$

Table 2-2. Levels of Significant Exposure to Cadmium - Oral (continued)

Key to[a] figure	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
58	Rat (Sprague-Dawley)	6 wk 5 d/wk 1 x/d (GW)	Hepatic	0.25 M			Muller et al. 1988 Cd acetate
			Bd Wt	0.25 M			
59	Rat (NS)	4 wk (W)	Hemato			0.8 F (decreased hematocrit and hemoglobin)	Ogoshi et al. 1989 $CdCl_2$
			Musc/skel		0.8 F (decreased bone strength in young animals)		
			Bd Wt	0.8	1.6 F (10% decreased body weight gain)		
60	Rat (Long- Evans)	5 mo (W)	Cardio		0.0081 F (15 mmHg increase in systolic blood pressure)		Perry et al. 1989 $CdCl_2$
			Bd Wt	0.0081 F			
61	Rat (NS)	200 d (W)	Resp	0.6 M	1.2 M (reduced static compliance, lung lesions)		Petering et al. 1979 $CdCl_2$
62	Rat (Sprague-Dawley)	120 d (W)	Resp			3.62 M (emphysema)	Petering et al. 1979 $CdCl_2$
63	Rat (Sprague-Dawley)	111 d (90 d prior to Gd 1 through Gd 21) (W)	Hemato	5.23 F			Petering et al. 1979 $CdCl_2$

Table 2-2. Levels of Significant Exposure to Cadmium - 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
64	Rat (Long- Evans)	14 wk (W)	Hepatic	5.8 M			Pleasants et al. 1992 $CdCl_2$
			Hemato		2.9 M (decreased neutrophils and monocytes, increased lymphocytes)		
			Musc/skel			2.9 M (osteoporosis)	
			Bd Wt	2.9 M	5.8 (21% increased relative kidney weight)		
			Bd Wt	2.9 M		5.8 M (22% decreased body weight gain)	
65	Rat (Long- Evans)	14 wk (W)	Hemato			11.6 M (decreased hematocrit and erythrocyte counts)	Pleasants et al. 1993 $CdCl_2$
			Hepatic	11.6 M			
			Renal		11.6 M (increased relative kidney weight)		
			Bd Wt			11.6 M (44% decreased body weight gain)	
66	Rat (Sprague-Dawley)	21-25 d Gd 1-Ld 1 (F)	Bd Wt			19.7 F (77-80% decreased maternal weight gain)	Pond and Walker 1975 $CdCl_2$
67	Rat (Wistar)	90 d (W)	Resp	16 F			Prigge 1978a $CdCl_2$
			Hemato		4 F (23% decreased serum iron, 21% decreased serum alkaline phosphatase)		
			Renal	4 F		8 F (35% increase in urine protein)	
			Bd Wt	8 F			

Table 2-2. Levels of Significant Exposure to Cadmium - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
68	Rat (Wistar)	12, 26, 50, or 100 d (W)	Hemato			12 M (iron deficient anemia)	Sakata et al. 1988 $CdCl_2$
69	Rat (Sprague-Dawley)	2-6 wk 5 d/wk 1 x/d (G)	Bd Wt	0.250 M			Stacey et al. 1988a Cd acetate
70	Rat (Sprague-Dawley)	6 wk (W)	Bd Wt	0.4 M			Stacey et al. 1988a $CdCl_2$
71	Rat (ITRC)	15-60 d (F)	Hepatic		5M (reduced glycogen, increased G6PD and FDP)		Tewari et al. 1986b $CdCl_2$
			Renal		5M (reduced AST and ALT activity, increased G6PD and FDP activity)		
72	Rat (Sprague-Dawley)	7-12 mo (W)	Renal	13 F			Viau et al. 1984 $CdCl_2$
			Bd Wt	13 F			

Table 2-2. Levels of Significant Exposure to Cadmium - 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
73	Rat (NS)	100 d (F)	Cardio		2.79 M (muscle hypertrophy, increased weight, some fibrous tissue)		Wilson et al. 1941 $CdCl_2$
			Hemato			2.79 M (severe anemia)	
			Hepatic		2.79 M (focal necrosis with some fibrous tissue)		
			Renal		2.79 M (slight tubular epithelial swelling and casts)		
			Endocr		2.79 M (pancreatic atrophy and pancreatitis)		
			Bd Wt		2.79 M (12% decreased body weight)	5.58 M (33% decreased body weight)	
74	Mouse (C57BL/6)	3-11 wk (W)	Bd Wt			12.5 M (63% decreased body weight gain)	Malave and de Ruffino 1984 $CdCl_2$
75	Mouse (B6C3F1)	16-46 wk (W)	Bd Wt			232 M (45% decreased body weight)	Waalkes et al. 1993 $CdCl_2$
76	Mouse (QS/CH)	Gd 1-19 (W)	Hemato	4.8 F		9.6 F (anemia)	Webster 1978 $CdCl_2$
			Bd Wt	4.8 F	9.6 F (14% decrease in maternal weight gain)		
77	Dog (Beagle)	3 mo (F)	Cardio	0.75			Loeser and Lorke 1977b $CdCl_2$
			Hemato	0.75			
			Hepatic	0.75			
			Renal	0.75			
			Bd Wt	0.75			

Table 2-2. Levels of Significant Exposure to Cadmium - 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
78	Rabbit (New Zealand)	9 mo (W)	Cardio		1.6 M (increased aortic resistance, reduced contractility)		Boscolo and Carmignani 1986 $CdCl_2$
			Renal	1.6 M			
			Bd Wt	1.6 M			
79	Rabbit (New Zealand and Belgian Giant)	200 d (W)	Hemato			14.9 M (anemia)	Stowe et al. 1972 $CdCl_2$
			Hepatic			14.9 M (focal hepatic fibrosis and biliary hyperplasia)	
			Renal			14.9 M (tubular necrosis, glomerular and interstitial fibrosis)	
			Endocr	14.9			
			Bd Wt		14.9 M (11% decrease in body weight)		
80	Rabbit (New Zealand)	34 d (W)	Cardio			0.07 F (hypertension: increased arterial pressure (>50 mmHg) and increased ventricular mass)	Tomera and Harakal 1988 Cd acetate
			Bd Wt	0.07 F			
	Immunological/Lymphoreticular						
81	Monkey (Rhesus)	10 wk (F)			5 M (increased cell-mediated immune response)		Chopra et al. 1984 $CdCl_2$
82	Rat (Wistar)	170 d (W)			28 F (biphasic decrease then increase in natural killer cell activity)		Cifone et al. 1989a $CdCl_2$

Table 2-2. Levels of Significant Exposure to Cadmium - 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
83	Rat (Wistar)	3 mo (F)		3.0			Loeser and Lorke 1977a $CdCl_2$
84	Rat (Long- Evans)	14 wk (W)		5.8 M			*Pleasants et al.* 1992 $CdCl_2$
85	Rat (Sprague-Dawley)	2-6 wk 5 d/wk 1 x/d (G)			0.250 M (increased blastogenesis)		Stacey et al. 1988a Cd acetate
86	Rat (Sprague-Dawley)	6 wk (W)			0.4 M (increased blastogenic activity)		Stacey et al. 1988a $CdCl_2$
87	Mouse (BDF1)	3 wk (W)		1.4 F	2.8 F (decreased humoral immune response)		*Blakley 1985* $CdCl_2$
88	Mouse (Swiss)	280 d (W)				1.9 F (greater susceptibility to murine lymphocytic leukemia virus)	*Blakley 1986* $CdCl_2$
89	Mouse (BDF1)	26 d (W)		12.5 F			Blakley 1988 $CdCl_2$
90	Mouse (Swiss-Webster)	30 d (W)		22 M			Bouley et al. 1984 Cd acetate
91	Mouse (Swiss-Webster)	10 wk (W)		57 M			Exon et al. 1986 $CdCl_2$, Cd acetate

Table 2-2. Levels of Significant Exposure to Cadmium - 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
92	Mouse (C57BL/6N)	12-16 wk (W)		19 F	57 F (reduced number of SRBC-activated, plaque-forming cells)		Krzystyniak et al. 1987 $CdCl_2$
93	Mouse (C57BL/6)	3-11 wk (W)			12.5 M (decreased suppressor cell activity)		Malave and de Ruffino 1984 $CdCl_2$
94	Mouse (ICR)	10 wk (W)			0.75 M (induction of anti-nuclear autoantibodies)		Ohsawa et al. 1988 $CdCl_2$
	Neurological						
95	Rat (Wistar)	14 wk 5 d/wk (GW)		4 F	40 F (aggressive behavior)		Baranski and Sitarek 1987 $CdCl_2$
96	Rat (Sprague-Dawley)	3-24 wk (W)		1.2 M	3.1 M (decreased motor activity)		Kotsonis and Klaassen 1978 $CdCl_2$
97	Rat (Wistar)	90 d (W)			24 M (increased brain dopamine levels; decreased 5-HT, SDH, MAO, and ATPase levels)		Murthy et al. 1989 Cd acetate
98	Rat (Sprague-Dawley)	55 d (F)		1 M	5 M (increased passive avoidance)		Nation et al. 1984 $CdCl_2$
99	Rat (Sprague-Dawley)	60 d (F)			9 M (decreased motor activity)		Nation et al. 1990 $CdCl_2$

Table 2-2. Levels of Significant Exposure to Cadmium - 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
100	Mouse (QS)	22 wk (W)		0.2 F		1.4 F (necrosis of choroid plexus epithelial cells)	Valois and Webster 1989 $CdCl_2$
	Reproductive						
101	Rat (Wistar)	20 d Gd 1-20 (W)		28.8 F			Baranski 1987 $CdCl_2$
102	Rat (Wistar)	14 wk 5 d/wk (GW)		4 F		40 F (increased duration of estrus cycle)	Baranski and Sitarek 1987 $CdCl_2$
103	Rat (Wistar)	11 wk 5 d/wk (GW)		4 F			Baranski et al. 1983 $CdCl_2$
104	Rat (Wistar)	10 wk 1 x/wk (GW)		5 M			Bomhard et al. 1987 $CdCl_2$
105	Rat (Sprague-Dawley)	12 wk (W)				8.58 M (necrosis and atrophy of seminiferous tubule epithelium)	Cha 1987 $CdCl_2$
106	Rat	4 wk (F)		2.5			Groten et al. 1990 $CdCl_2$
107	Rat (Sprague-Dawley)	22 d Gd 0-21 (W)		3.8 F			Kelman et al. 1978 form not specified
108	Rat (albino)	4 wk (W)		4.8 F			Kostial et al. 1993 $CdCl_2$

Table 2-2. Levels of Significant Exposure to Cadmium - 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
109	Rat (Sprague-Dawley)	24 wk (W)		8.0 M			Kotsonis and Klaassen 1978 $CdCl_2$
110	Rat (Wistar)	3 mo (F)		3.0			Loeser and Lorke 1977a $CdCl_2$
111	Rat (Sprague-Dawley)	60 d prior to Gd 1 or Gd 1-Gd 21 (W)		2.61 F			Petering et al. 1979 $CdCl_2$
112	Rat (Sprague-Dawley)	111 d (90 d prior to Gd 1 through Gd 21) (W)		5.23 F			Petering et al. 1979 $CdCl_2$
113	Rat (Long- Evans)	14 wk (W)		2.9 M	5.8 M (28% increased relative testes weight)		Pleasants et al. 1992 $CdCl_2$
114	Rat (Long- Evans)	14 wk (W)			11.6 M (64% increased relative weight of testes)		Pleasants et al. 1993 $CdCl_2$
115	Rat (Sprague-Dawley)	21-25 d Gd 1-Ld 1 (F)		19.7 F			Pond and Walker 1975 $CdCl_2$
116	Rat (NS)	120 d (W)				12.6 M (decreased sperm count and motility, seminiferous tubular damage)	Saxena et al. 1989 Cd acetate

Table 2-2. Levels of Significant Exposure to Cadmium - 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
117	Rat (Sprague-Dawley)	9 wk 7 d/wk 1 x/d (GW)		1.0		10	(>50% fewer copulating and pregnant females, 50% reduction in number of live fetuses)	Sutou et al. 1980 *form not specified*
118	Rat (Long- Evans)	70-80 d (W)		4.64 M				Zenick et al. 1982 $CdCl_2$
119	Mouse (CD)	6 mo (W)				2.5	(reproductive failure)	Schroeder and Mitchener 1971 Unspecified Cd
120	Dog (Beagle)	3 mo (F)		0.75				Loeser and Lorke 1977b *$CdCl_2$*
	Developmental							
121	Rat (Wistar)	21 d Gd 1-21 (W)				0.706	(delayed development of sensory motor coordination reflexes; increased motor activity)	*Ali et al. 1986* Cd acetate
122	Rat (Wistar)	20 d Gd 1-20 (W)				9.6	(decreased fetal body weight [12%], body length [7%], and hematocrit [13%])	Baranski 1987 $CdCl_2$
123	Rat (Wistar)	11 wk 5 d/wk 1 x/d (GW)			0.04 (pup behavioral alterations)			Baranski et al. 1983 $CdCl_2$

Table 2-2. Levels of Significant Exposure to Cadmium - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg)	LOAEL Less Serious (mg/kg)	LOAEL Serious (mg/kg)	Reference Chemical Form
124	Rat (Wistar)	11-94 d Gd 5-15 Ld 2-28 1 x/d ppd 1-56 5 d/wk 1 x/d (GW)				14.0 M (decr. horizontal ambulation and rearing activity; incr. frequency of somatosensory, visual, and auditory electrocorticogram; prolonged latency and duration of evoked potentials)	Desi et al. 1998 $CdCl_2$
125	Rat (Druckery)	42 d Gd 0- Ld 21 (W)				5.0 (decreased pup brain and body weight at 7, 14, and 21 days)	Gupta et al 1993 Cd acetate
126	Rat (Sprague-Dawley)	21 d Gd 0-20 (W)				1.5 (12% decreased hematocrit)	Kelman et al. 1978 form not specified
127	Rat (albino)	10 wk (W)			4.8 (12% decrease in pup body weight at weaning)		Kostial et al. 1993 $CdCl_2$
128	Rat (Wistar)	approx. 49 d 4 wks of age thru mating 7 d/wk 1 x/d addt. 49 days gestation thru parturition 5 d/wk (GO)				7.0 M (alterations in ambulation behavior; prolonged latency and duration of somatosensory evoked potentials)	Nagymajtenyi et al. 1997 $CdCl_2$

Table 2-2. Levels of Significant Exposure to Cadmium - 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
129	Rat (Sprague-Dawley)	60 d prior to Gd 1 or Gd 1-21 (W)			2.61 (decreased live birth weight)		Petering et al. 1979 $CdCl_2$
130	Rat (Sprague-Dawley)	111 d (90 d prior to Gd 1-21) (W)			0.56 (reduction in neonate copper levels)		Petering et al. 1979 $CdCl_2$
131	Rat (Sprague-Dawley)	22 d Gd 1-Ld 1 (F)			19.7 (13-19% decreased pup birth weight)		Pond and Walker 1975 $CdCl_2$
132	Rat (ITRC)	21 d Gd 0-20 (W)		21			Saxena et al. 1986 Cd acetate
133	Rat (Sprague-Dawley)	15 d Gd 6-20 (W)		0.63	4.7 (8% decreased fetal body weight)		Sorell and Graziano 1990 $CdCl_2$
134	Rat (Sprague-Dawley)	9 wk 1 x/d (GW)		1.0	10 (delayed ossification, decreased body weight)		Sutou et al. 1980 form not specified
135	Mouse (CD)	6 mo (W)				2.5 (malformation-sharp angulation of the distal third of the tail; increased mortality)	Schroeder and Mitchener 1971 Unspecified Cd
136	Mouse (QS/CH)	19 d Gd 1-19 (W)				2.4 (decreased fetal body weight; severe anemia)	Webster 1978 $CdCl_2$

Table 2-2. Levels of Significant Exposure to Cadmium - 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
137	Mouse (Wistar)	3.5 mo (W)		5.7	14.25 (increased lipid peroxide in brain, liver, and heart of 7-day old pups)		Xu et al. 1993b form not specified
	Cancer						
138	Mouse (Swiss)	280 d (W)				1.9 F (CEL: small increase in mammary tumors in leukemia prone mice)	Blakley 1986 $CdCl_2$
	CHRONIC EXPOSURE						
	Systemic						
139	Human	NS lifetime (F)	Renal	0.0021 [b]			Nogawa et al. 1989 form not specified
140	Human	>25 yr lifetime (environ)	Hemato	0.0078			Shiwen et al. 1990 Cd metal
			Musc/skel	0.0078			
			Renal			0.0078 (renal tubule interstitial lesions)	
141	Monkey (Rhesus)	9 yr (F)	Cardio	0.53 M	1.71 M (increased blood pressure during the first 1.5 years)		Akahori et al. 1994 $CdCl_2$

Table 2-2. Levels of Significant Exposure to Cadmium - 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
142	Monkey (Rhesus)	9 yr (F)	Resp	4.0 M			Masaoka et al. 1994 $CdCl_2$
			Hemato			4.0 M (anemia)	
			Musc/skel			4.0 M (marked decrease in body length)	
			Renal	0.4 M		4.0 M (proteinuria, glucosuria)	
			Bd Wt	0.12 M	0.4 M (decreased body weight from decreased food intake)	4.0 M (markedly decreased growth rate)	
143	Rat (Sprague-Dawley)	18 mo (W)	Renal			13 F (loss of glomerular polyanion charge barrier, proteinuria)	Bernard et al. 1992 $CdCl_2$
144	Rat (Wistar)	72 wk (F)	Renal	3.5		17.5 (8 to 9-fold increase in LDH and GST starting at 13 weeks)	Bomhard et al. 1984 $CdCl_2$
145	Rat (Sprague-Dawley)	12 mo (W)	Hemato	0.79			Decker et al. 1958 $CdCl_2$
			Bd Wt	0.79			
146	Rat (Sprague-Dawley)	M: 92 wk F: 84 wk (W)	Cardio	4.01			Fingerle et al. 1982 $CdCl_2$
			Renal	0.8		1.51 (proximal tubule lesions)	
			Bd Wt	4.01			
147	Rat (Long- Evans)	18 mo (W)	Cardio			0.01 F (hypertension, 20% increase in systolic pressure)	Kopp et al. 1982 Cd acetate
			Hepatic	0.65 F			

Table 2-2. Levels of Significant Exposure to Cadmium - 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
148	Rat (Sprague-Dawley)	6, 12, or 18 mo (W)	Cardio	2.281 F			Mangler et al 1988 $CdCl_2$
			Hepatic	2.281 F			
			Renal			2.337 F (cloudy swelling of tubular cells)	
			Bd Wt	2.281 F			
149	Rat (Wistar)	31 mo (W)	Musc/skel			3.6 (muscle atrophy)	Sato et al. 1978 $CdCl_2$
			Bd Wt	3.6			
150	Rat (Wistar)	2 yr (W)	Renal	2.6 M			Shaikh et al. 1989 $CdCl_2$
151	Rat (Wistar)	77 wk (F)	Bd Wt	3.5 M	7.0M (10% decreased body weight)		Waalkes and Rehm 1992 $CdCl_2$
152	Mouse (CBA/H)	12 mo (W)	Hemato			57 (anemia and bone marrow hypoplasia)	Hays and Margaretten 1985 form not specified
			Renal	57			
			Bd Wt			57 (21% decreased terminal body weight)	
	Neurological						
153	Rat (Wistar)	31 mo (W)				3.6 (peripheral neuropathy)	Sato et al. 1978 $CdCl_2$

Table 2-2. Levels of Significant Exposure to Cadmium - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL			Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
	Cancer							
154	Rat (Wistar)	77 wk (F)				3.5 M	(CEL: increased rates of prostatic adenomas)	Waalkes and Rehm 1992 $CdCl_2$

[a]The number corresponds to entries in Figure 2-2

[b]Used to derive a chronic-duration oral minimal risk level (MRL) of $2x10^{-4}$ mg/kg/day based upon kidney effects. A threshold of lifetime intake of 110 µg/g (2,000 mg Cd for a 50-year lifetime) was found for renal damage. A NOAEL of 0.0021 mg/kg/day was derived from this value by dividing by 53 kg (average weight) and 50 years (364 days/year). The MRL is based on this NOAEL and an uncertainty factor of 10 to account for sensitive members of the population.

Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); endocr = endocrine; environ = environmental; F = female; (F) = food; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day(s); (GW) = gavage in water; GST = glutathione transferase; (IN) = ingestion; Hb = hemoglobin; Hemato = hematological; Ht = hematocrit; 5-HT = 5-hydroxytryptamine; Ld = lactational day; LD_{50} = lethal dose, 50% kill; LDH = lactate dehydrogenase; LOAEL = lowest-observed-adverse-effect level; M = male; metab = metabolic; MAO = monoamine oxidase; mo = month; Musc/skel = muscular/skeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; SDH = succinic dehydrogenase; (W) = water; wk = week(s); x = times; yr = year(s)

Figure 2-2. Levels of Significant Exposure to Cadmium - Oral

Acute (≤14 days)

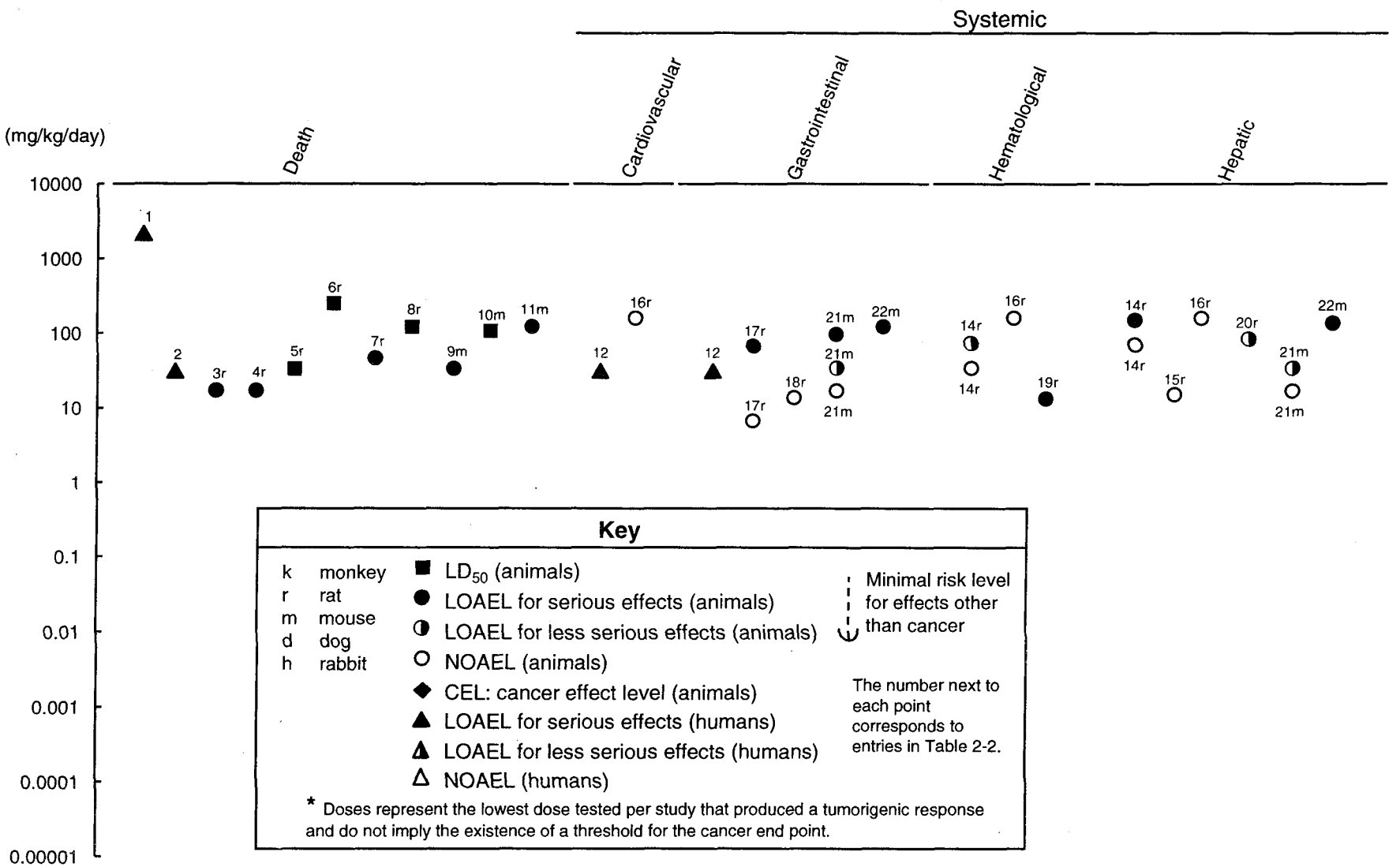


Figure 2-2. Levels of Significant Exposure to Cadmium - Oral (cont.)

Acute (≤14 days)

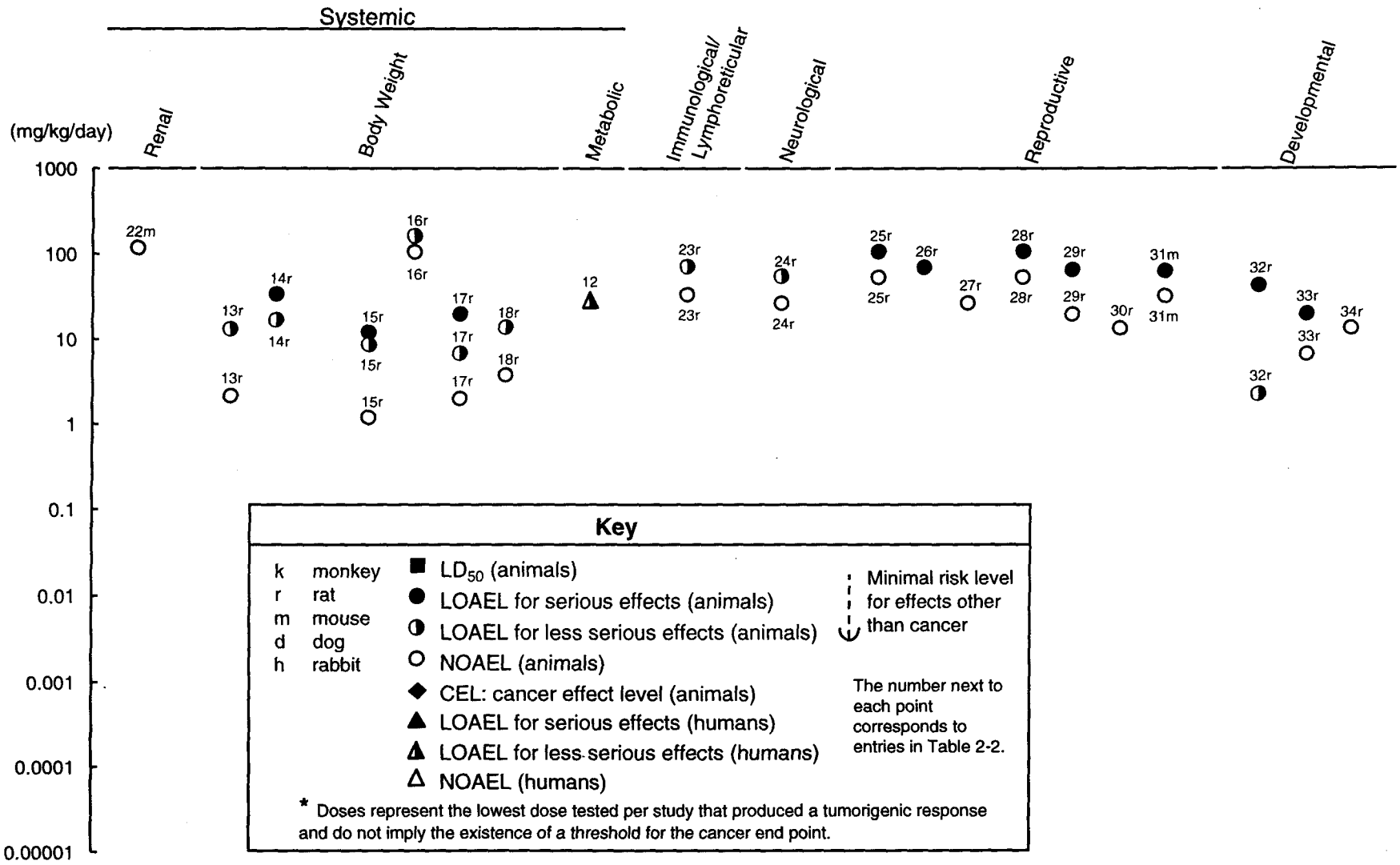


Figure 2-1. Levels of Significant Exposure to Cadmium - Oral (cont.)

Intermediate (15-364 days)

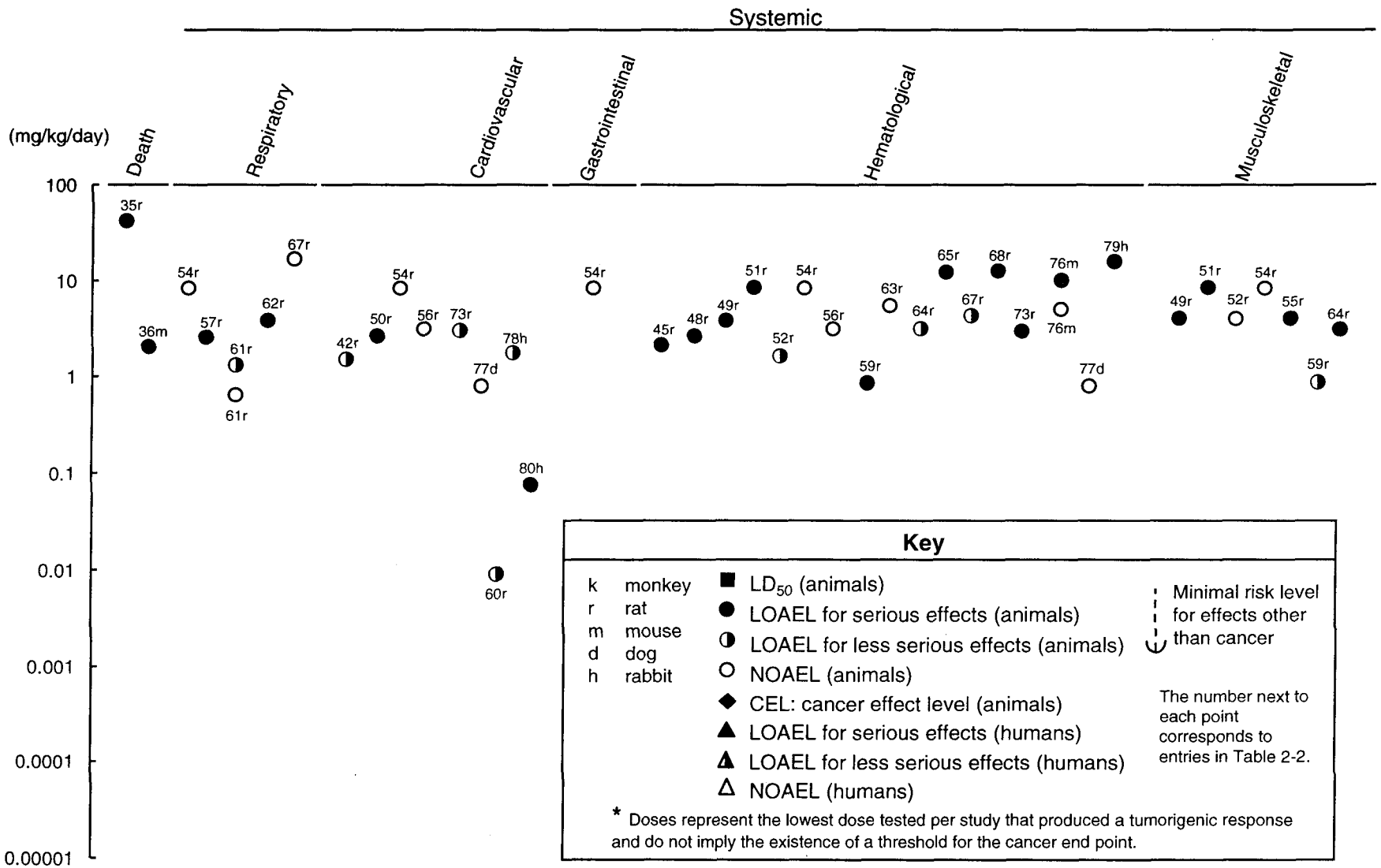


Figure 2-2. Levels of Significant Exposure to Cadmium - Oral (cont.)

Intermediate (15-364 days)

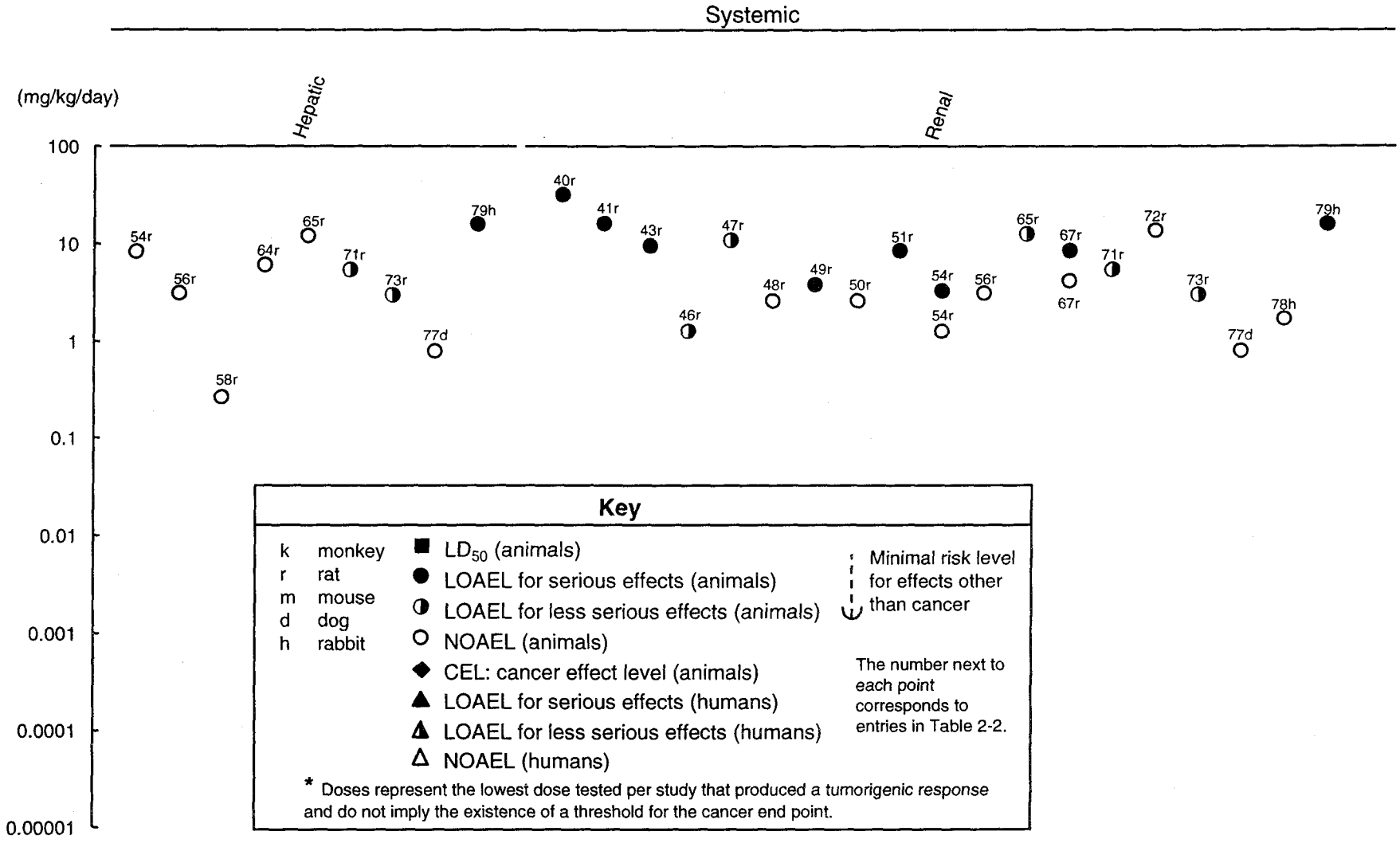


Figure 2-2. Levels of Significant Exposure to Cadmium - Oral (cont.)

Intermediate (15-364 days)

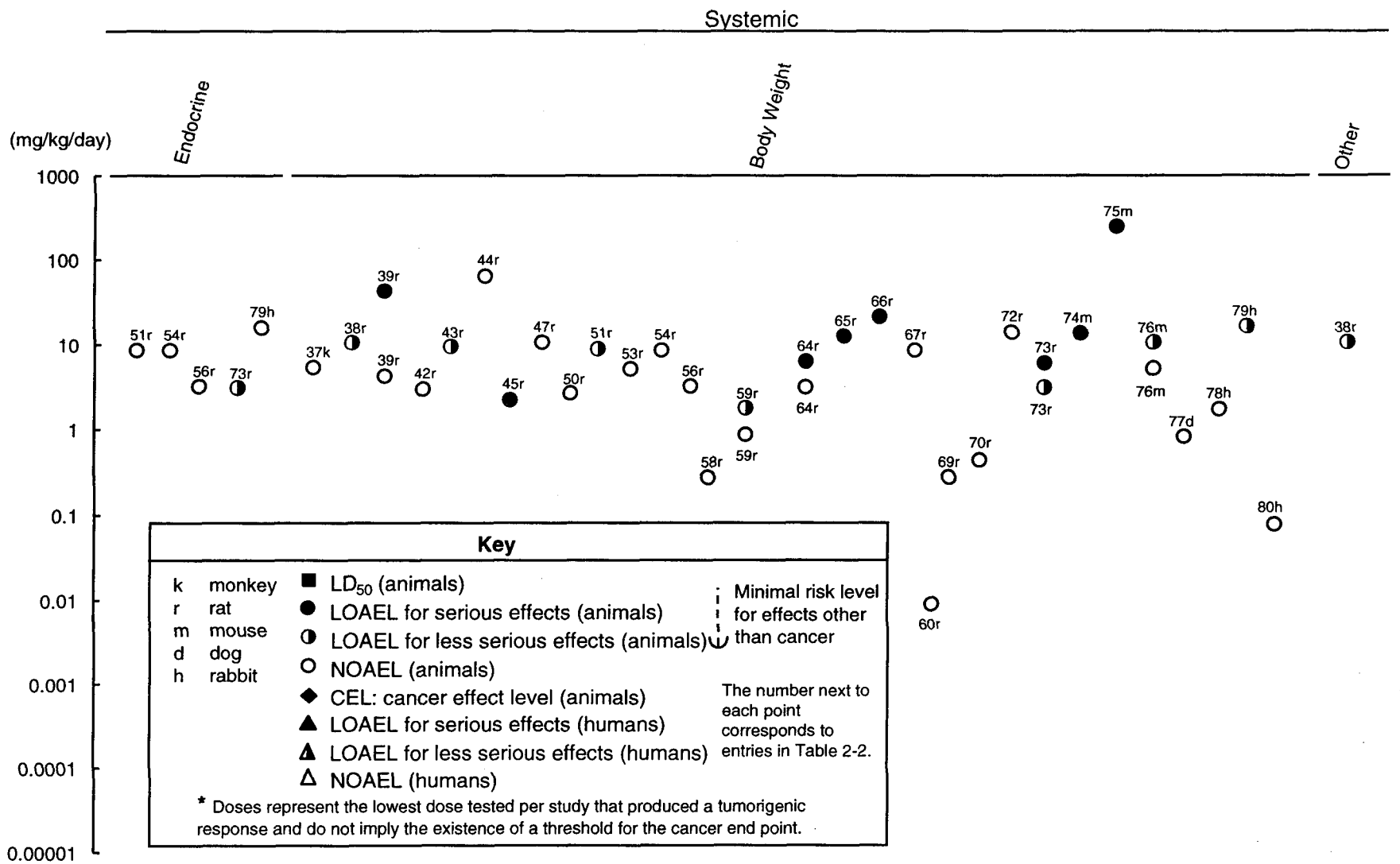


Figure 2-2. Levels of Significant Exposure to Cadmium - Oral (cont.)

Intermediate (15-364 days)

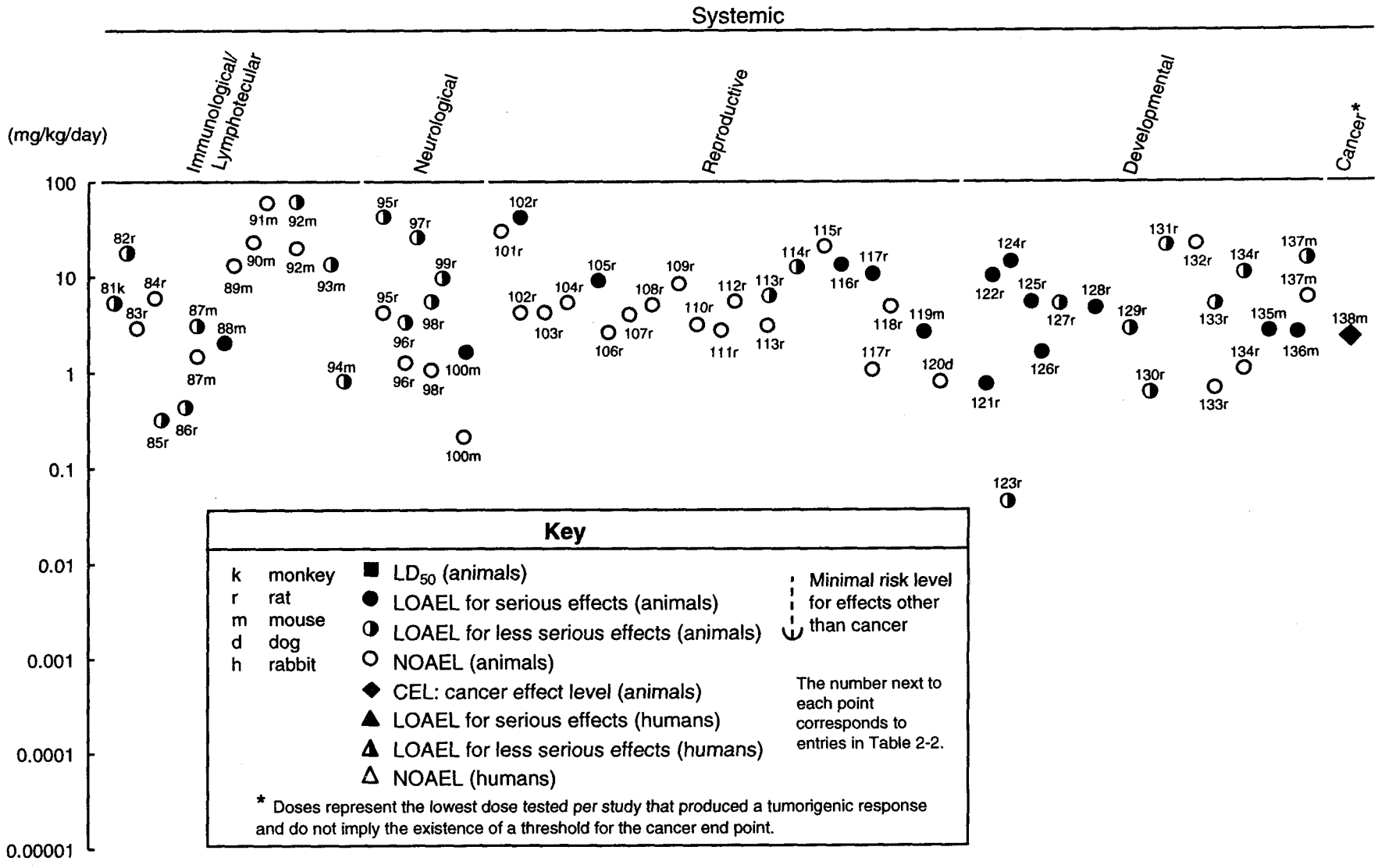
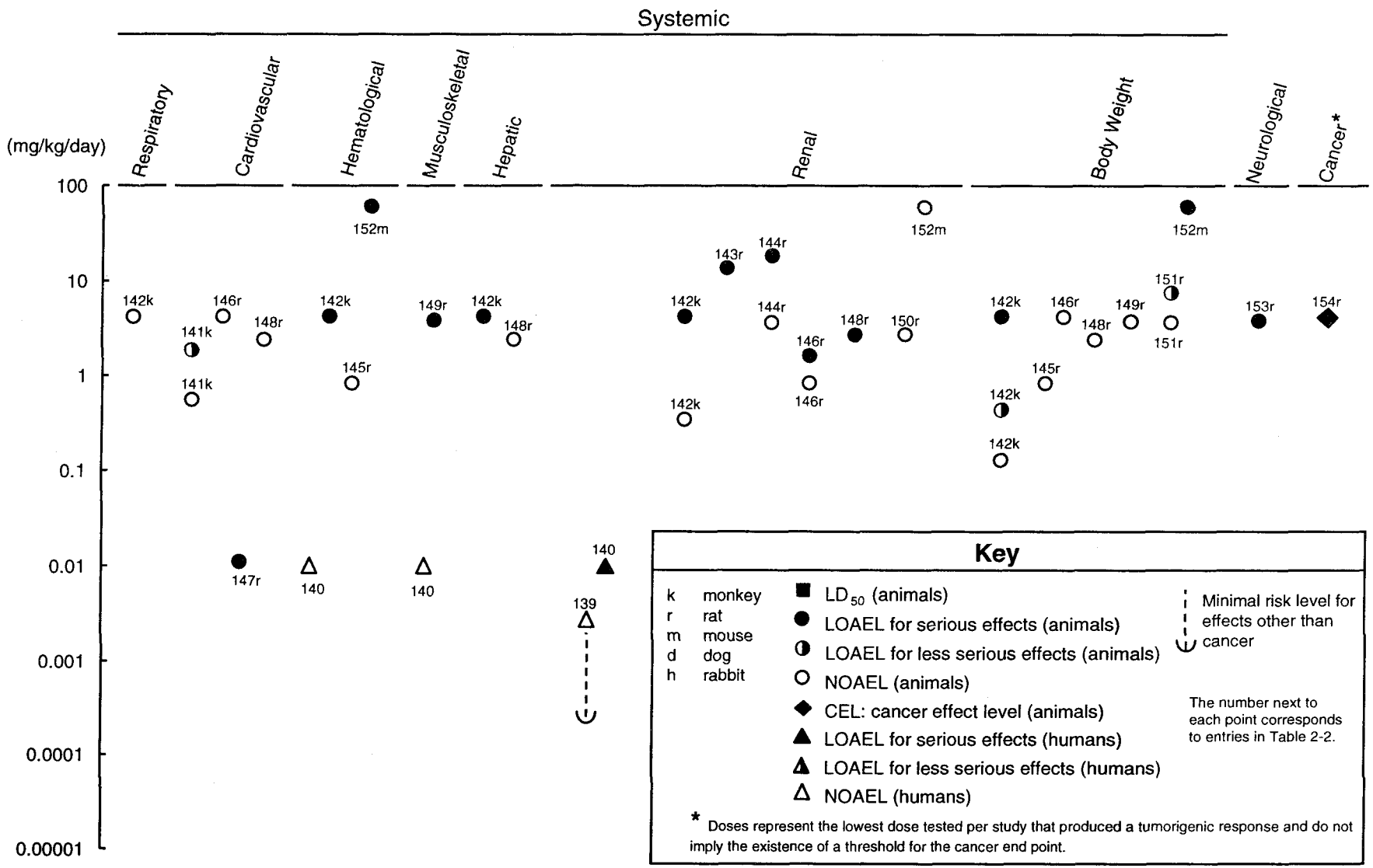


Figure 2-2. Levels of Significant Exposure to Cadmium - Oral (cont.)

Chronic (≥365 days)



2.2.2.2 Systemic Effects

Representative NOAEL and LOAEL values for systemic effects of oral exposure to cadmium in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

Respiratory Effects. No studies were located regarding respiratory effects in humans after oral exposure to cadmium.

No respiratory effects were observed in Rhesus monkeys from 4 mg/kg/day of cadmium chloride in the food for 9 years (Masaoka et al. 1994). A dose-dependent decrease in relative lung weight was observed in male rats after gavage exposure to cadmium chloride for 10 days, but not in female rats after gavage exposure, or in male and female rats after drinking-water exposure (Borzelleca et al. 1989). Intermediate duration oral exposure caused fibrosis in lungs of rats exposed to 2.4 mg Cd/kg/day of cadmium chloride after 6 and 16 weeks (Miller et al. 1974b). Petering et al. (1979) observed a reduced static compliance and lung lesions (not specified) in male Sprague-Dawley rats exposed to 1.2 mg Cd/kg/day in water for 200 days. Zinc-deficient rats were more susceptible to lung lesions from exposure to $CdCl_2$ (Petering et al. 1979). Rats exposed to $CdCl_2$ at 3.62 mg Cd/kg/day in the drinking water for 120 days developed emphysema (Petering et al. 1979). No histopathologic lesions of the lung were found in male Sprague-Dawley rats after 24 weeks of exposure to cadmium in drinking water at a maximum dose of 8 mg/kg/day (Kotsonis and Klaassen 1978). Lung weight was unchanged in Wistar rats after 90 days of exposure in drinking water at 16 mg/kg/day (Prigge 1978a). Effects on the lung following oral exposure to cadmium may be secondary to systemic changes (Petering et al. 1979); however, the studies that found lung effects did not examine other systemic effects in the exposed rats (Miller et al. 1974b; Petering et al. 1979).

Cardiovascular Effects. Studies regarding cardiovascular effects in humans after oral exposure to cadmium have primarily investigated relationships between blood pressure and biomarkers of cadmium exposure such as cadmium levels in blood, urine, or other tissues. Smoking is an important confounding factor, because of the higher blood, urine, and tissue cadmium levels of smokers (see Section 2.3) and the known cardiovascular toxicity of cigarette smoking. Case-control and cohort epidemiologic studies that adequately control for smoking have typically found no association between body cadmium levels (primarily reflecting dietary exposure) and hypertension (Beevers et al. 1980; Cummins et al. 1980; Ewers et al. 1985; Lazebnik et al. 1989; Shiwen et al. 1990); however, some studies have found positive

correlations (Geiger et al. 1989; Tulley and Lehmann 1982) or negative correlations (Kagamimori et al. 1986; Staessen et al. 1984). Similar conflicting findings have been reported in studies analyzing death rates from cardiovascular disease among populations with dietary cadmium exposure (Inskip and Beral 1982; Shigematsu 1984). Disorders of the cardiac conduction system, lower blood pressure, and decreased frequency of cardiac ischemic changes were found among elderly women with past high dietary exposure to cadmium (Kagamimori et al. 1986). Rhythmic disturbances, including ventricular fibrillation, were seen in an individual who had ingested 25 mg/kg cadmium as cadmium iodide (Wisniewska-Knypl et al. 1971).

A single gavage dose of 150 mg/kg cadmium in male Sprague-Dawley rats had no effect on blood pressure (Kotsonis and Klaassen 1977). Oral exposure of rats, rabbits, and monkeys to cadmium over intermediate and chronic durations has been found to increase blood pressure in some studies (Akahori et al. 1994; Boscolo and Carmignani 1986; Carmignani and Boscolo 1984; Kopp et al. 1982; Perry et al. 1989; Tomera and Harakal 1988), but not in others (Fingerle et al. 1982; Kotsonis and Klaassen 1978; Loeser and Lorke 1977a, 1977b; Mangler et al. 1988; Wills et al. 1981). In general, studies showing an effect on blood pressure have had control groups with lower blood pressure than studies showing no effect, and observed increases in blood pressure are generally small. At least in rats, the effect on blood pressure appears to be biphasic, reaching a maximum effect (an increase of 12-14 mm Hg in average systolic pressure) at intakes of 0.07 mg/kg/day, but decreasing to normal or even below normal at intakes 10-100 times higher (Kopp et al. 1982). Enlarged and arteriosclerotic hearts have been found in rats orally exposed to 0.35 mg Cd/kg/day for 3 years (Schroeder et al. 1965) or to 2.79 mg Cd/kg/day for 100 days (Wilson et al. 1941), but this effect is likely to be secondary to cadmium-induced anemia (Wilson et al. 1941). Histopathologic lesions of heart tissues (congestion, separation of muscle fibers) and decreased activity of antioxidant enzymes, but no increase in peroxidation, were found among rats given 2.5 mg/kg/day of cadmium in the diet for 7 weeks (Jamall et al. 1989). Overall, the evidence for cardiovascular toxicity resulting from oral exposure to cadmium is suggestive of a slight effect.

Gastrointestinal Effects. Numerous human and animal studies indicate that oral exposure to cadmium in high concentrations causes severe irritation to the gastrointestinal epithelium (Andersen et al. 1988; Frant and Kleeman 1941). Common symptoms in humans following ingestion of food or beverages containing high concentrations of cadmium include nausea, vomiting, salivation, abdominal pain, cramps, and diarrhea (Baker and Hafner 1961; Buckler et al. 1986; Frant and Kleeman 1941; Nordberg et al. 1973; Shipman 1986; Wisniewska-Knypl et al. 1971). Although exact doses have not been measured, gastrointestinal symptoms have been caused in children by 16 mg/L cadmium in soft drinks (Nordberg et

al. 1973) and 13 mg/L cadmium in popsicles (Frant and Kleeman 1941). Assuming an intake of 0.15 L (Nordberg et al. 1973) and a body weight of 35 kg, the emetic dose is 0.07 mg/kg. Although few studies have specifically examined gastrointestinal effects of longer-term cadmium exposure, no surveys of environmentally exposed populations have reported gastrointestinal symptoms (Morgan and Simms 1988; Roels et al. 1981a; Shigematsu 1984).

In rats and mice, histopathologic lesions (e.g., severe necrosis, hemorrhage, ulcers) in the gastrointestinal epithelium have been observed after high (>30 mg/kg/day) acute-duration oral cadmium exposure by gavage (Andersen et al. 1988; Basinger et al. 1988; Machemer and Lorke 1981), but not after lower levels (8 mg/kg/day in drinking water) for 24 weeks (Kotsonis and Klaassen 1978).

Hematological Effects. Oral cadmium exposure reduces gastrointestinal uptake of iron, which can result in anemia if dietary intake of iron is low. Anemia has been found in some instances among humans with chronic dietary exposure to cadmium (Kagamimori et al. 1986), but other studies have found no significant relationship between dietary cadmium exposure and anemia in humans (Roels et al. 1981a; Shiwen et al. 1990). Hypoproteinemia and hypoalbuminemia were reported in a male who ingested 25 mg/kg cadmium as cadmium iodide (Wisniewska-Knypl et al. 1971).

A number of studies have demonstrated that oral exposure to cadmium frequently produces anemia in laboratory animals, and that additional iron prevents anemia (Decker et al. 1958; Groten et al. 1990; Hays and Margaretten 1985; Itokowa et al. 1974; Kawamura et al. 1978; Kelman et al. 1978; Kozlowska et al. 1993; Ogoshi et al. 1989; Pleasants et al. 1992, 1993; Pond and Walker 1972; Sakata et al. 1988; Sorell and Graziano 1990; Stowe et al. 1972; Watanabe et al. 1986; Webster 1978; Wilson et al. 1941). Decreases in serum iron have also been reported (Prigge 1978a). Borzelleca et al. (1989) reported slight but statistically significant increases in hemoglobin, hematocrit, and erythrocytes in male rats at 65.6 mg/kg/day once a day for 10 days, but no change in females. Male Sprague-Dawley rats receiving a single gavage dose of 150 mg/kg cadmium showed no signs of anemia 14 days later (Kotsonis and Klaassen 1977), but anemia was produced in male Wistar rats after 12 days of drinking-water exposure to 12 mg/kg/day (Sakata et al. 1988). Most intermediate-duration exposure studies in rats have shown evidence of anemia at doses of 2-14 mg/kg day (Decker et al. 1958; Groten et al. 1990; Itokawa et al. 1974; Kawamura et al. 1978; Pleasants et al. 1993; Pond and Walker 1972; Sakata et al. 1988; Wilson et al. 1941). However, some intermediate-duration studies have found no change in hemoglobin (Kotsonis and Klaassen 1978; Loeser and Lorke 1977a; Petering et al. 1979; Prigge 1978a) in rats treated at similar

doses. Anemia has also been seen in intermediate-duration studies in mice (Webster 1978) and rabbits (Stowe et al. 1972), but not in dogs (Loeser and Lorke 1977b). The result in dogs may be due to the relatively low dose of cadmium (0.75 mg/kg/day) used in this study. Hematological effects following chronic-duration oral exposure to cadmium are less well characterized. In monkeys maintained on 4 mg/kg/day cadmium in food, pale feces, and clinical signs of anemia occurred after 90 weeks, but the anemia was associated with a decreased food intake rather than an increase in reticulocytes (Masaoka et al. 1994). Anemia was not present in rats exposed via drinking water for 12 months to the relatively low dose of 0.79 mg/kg/day (Decker et al. 1958). The number of erythroid progenitor cells in bone marrow is decreased in mice exposed to 57 mg/kg/day of cadmium in drinking water for 12 months (Hays and Margaretten 1985), but is increased in rats exposed to 12 mg/kg/day of cadmium in drinking water for up to 100 days (Sakata et al. 1988). Thus, the question remains open whether factors in addition to reduced gastrointestinal absorption of iron such as direct cytotoxicity to marrow or inhibition of heme synthesis may contribute to anemia.

Musculoskeletal Effects. Painful bone disorders, including osteomalacia, osteoporosis, and spontaneous and painful bone fractures (an affliction called Itai-Itai or “ouch-ouch” disease), have been observed in some humans chronically exposed to cadmium in food. In the Jinzu River Basin, a cadmium contaminated area in Japan, osteomalacia and Itai-Itai disease have most often affected women with several risk factors such as poor nutrition and multiparity (Shigematsu 1984). Other Japanese populations with dietary cadmium exposure have also recently been found to have elevated osteoporosis and osteomalacia in both men and women (Kido et al. 1989b). The degree of loss of bone density is correlated with urinary excretion of β_2-microglobulin, an index of renal injury (see Section 2.5.2) (Kido et al. 1990a). Kagamimori et al. (1986) evaluated elderly Japanese women with heavy cadmium exposure from ingesting polluted drinking water, rice, and fish during World Wars I and II; and continued low-grade cadmium exposure from agricultural produce. Of 56 cases of Itai-itai disease, 26 were accompanied by osteomalacia and 26 were without osteomalacia.

Cadmium-exposed individuals exhibit a progressive disturbance in renal metabolism of vitamin D to its biologically active form (Nogawa et al. 1987, 1990) and an increased urinary excretion of calcium (Buchet et al. 1990). These results suggest that bone changes may be secondary to disruption in kidney of vitamin D metabolism and resulting imbalances in calcium absorption and excretion.

Studies in rats confirm that oral cadmium exposure may affect the skeleton. Decreased calcium content of bone and increased urinary calcium excretion are common findings in intermediate- and chronic-duration studies in the 2-8 mg Cd/kg/day range (Kawamura et al. 1978; Nogawa et al. 1981b; Pleasants et al. 1992; Watanabe et al. 1986). In contrast, Kotsonis and Klaassen (1978) reported no change in bone calcification after a 24-week exposure via drinking water at 8 mg/kg/day; and Kelman et al. (1978) reported no significant change in stable or radiolabeled calcium in any maternal rat tissues from a 3.8 mg/kg/day in drinking water for 22 days during gestation. Adverse effects on bone are exacerbated by a calcium-deficient diet (Itokawa et al. 1974; Kimura et al. 1974; Larsson and Piscator 1971; Wang and Bhattacharyya 1993; Wang et al. 1994), by exposure at a young age when bones are growing (Ogoshi et al. 1989), by ovariectomy (Bhattacharyya et al. 1988c), or by multiple rounds of gestation and lactation (Bhattacharyya et al. 1988b).

In the Ogoshi et al. (1989) study, the mechanical strength of femurs of young, adult, and elderly female rats was assessed after a 4-week exposure to $CdCl_2$ in drinking water. Young rats (21 days old; strain not specified; N=19-22F) were given $CdCl_2$ at 0, 5, or 10 ppm; adult rats (24 weeks old; strain not specified,; N=18-25NS) were given $CdCl_2$ at 0, 10, 20, 40, 80, or 160 ppm (adult rats); elderly rats (1.5 years old; strain not specified; N=25-27NS) were given $CdCl_2$ at or 0, 80, or 160 ppm. At the end of the 4-week exposure, femur compression and bending strengths, and cadmium and zinc content in bone were determined. Young rats had decreased bone strength at both doses tested, 5 and 10 ppm, while adult and elderly rats showed no effect up to doses of 160 ppm. Bone strength was correlated with cadmium content of bone but not cadmium content of liver or kidney. Young rats accumulated cadmium in the bones to a much greater extent (100 ng/g dry weight at 5 ppm, 150 ng/g at 10 ppm) then did the adult or elderly rats whose accumulation was roughly comparable and about 65 ng/g at the highest dose of 160 ppm.

In nonpregnant mice fed a calcium deficient diet, bone resorption was immediately and significantly increased by the addition of cadmium to the diet up to 25 ppm as evidenced by significant increases in fecal and serum cadmium (Wang and Bhattacharyya 1993). In pregnant mice fed a calcium deficient diet, an Itai-Itai like syndrome was produced from exposure to cadmium in the diet. Almost all of the calcium lost from the dam appeared in the pups, with 80% of that transferred via the dam’s milk during lactation and only 20% transferred during gestation (Wang et al. 1994). Some studies have detected effects in bone prior to development of proteinuria or histopathologic kidney damage in mice (Bhattacharyya et al. 1988a, 1988b; Ogoshi et al. 1989; Watanabe et al. 1986). These results raise the possibility that disturbed calcium metabolism may occur prior to proteinuria following long-term exposure to cadmium. For the

studies that establish thresholds for skeletal effects of cadmium exposure, NOAEL and LOAEL values for each species and duration category are listed in Table 2-2 and plotted in Figure 2-2.

Hepatic Effects. Liver damage is not usually associated with oral cadmium exposure, except at very high levels of exposure. In humans, a fatal dose of cadmium can cause pronounced liver damage (Buckler et al. 1986; Wisniewska-Knypl et al. 1971). Nishino et al. (1988) reported increased serum concentrations of the urea-cycle amino acids among individuals exposed to cadmium in the diet, and that these levels reflected liver as well as kidney damage. No other studies were located regarding hepatic effects in humans after oral exposure to cadmium.

Hepatic effects have been found in rats, mice, and rabbits after oral cadmium exposure. Acute exposure via gavage at doses of 30-138 mg/kg/day causes liver necrosis in most studies (Andersen et al. 1988; Basinger et al. 1988; Borzelleca et al. 1989; Shimizu and Morita 1990), although histopathologic evidence of liver damage was not seen in one study at a gavage dose of 150 mg/kg (Kotsonis and Klaassen 1977). Exposure of rats for 10 days to drinking water containing 13.9 mg Cd/kg/day was without effect on the liver (Borzelleca et al. 1989). Depletion of liver glutathione by fasting increases the liver necrosis following acute oral exposure to cadmium in rats (Shimizu and Morita 1990).

In a 10-week study, male Rhesus monkeys exposed to 4 mg/kg/day cadmium chloride via gavage, had a significant decrease in glutathione peroxidase in liver, kidney, heart, and lung in the following order: liver>kidney>heart>lung; a significant decrease in glutathione *S*-transferase (GST) activity towards 1-chloro-2,4-dinitrobenzene in all four organs in the following order: liver>lung>kidney>heart; and a significant increase in GST activity towards ethacrynic acid in all four organs in the following order: heart>lung>kidney>liver (Sidhu et al. 1993). Intermediate-duration exposure causes histopathologic changes in the liver (e.g., necrosis of central lobules, focal hepatic fibrosis, biliary hyperplasia) at doses of 1.6-15 mg/kg/day (Cha 1987; Gill et al. 1989b; Miller et al. 1974a; Schroeder et al. 1965; Stowe et al. 1972; Wilson et al. 1941), and metabolic alterations (e.g., decreased cytochrome c oxidase activity in mitochondria, increased ALT and AST activities) at doses of 0.05-10 mg/kg/day (Groten et al. 1990; Muller and Stacey 1988; Muller et al. 1988; Sporn et al. 1970; Steibert et al. 1984; Tewari et al. 1986b). Decreased relative liver weight to body weight has also been reported in male rats fed 5.95 mg/kg/day for 6 weeks (Kozlowska et al. 1993).

Other intermediate and chronic duration studies have not found liver effects in animals following oral exposure. These studies include a daily gavage exposure of 14 mg/kg/day for 6 weeks in rats (Hopf et al. 1990), a 3-month exposure to cadmium in food at 3 mg/kg/day in rats (Loeser and Lorke 1977a), a 24-week exposure to cadmium in water at 8 mg/kg/day in rats (Kotsonis and Klaassen 1978), and a 3-month exposure in food at 0.75 mg/kg/day in dogs (Loeser and Lorke 1977b). Kopp et al. (1982) report no hepatic effects from a chronic exposure of 18 months to cadmium in water at 0.65 mg/kg/day in rats. Representative NOAEL and LOAEL values for hepatic effects for each species and duration category are listed in Table 2-2 and plotted in Figure 2-2.

Renal Effects. Numerous studies indicate that the kidney is the main target organ of cadmium toxicity following extended oral exposure, with effects similar to those seen following inhalation exposure (see Section 2.2.1.2). Elevated incidences of tubular proteinuria have been found in numerous epidemiologic studies of residents of cadmium-polluted areas in Japan (Nogawa et al. 1980, 1989), Belgium (Buchet et al. 1990; Roels et al. 1981a), and China (Shiwen et al. 1990).

A recent study of Belgians (aged 20-80 years) from polluted and nonpolluted urban and rural areas found abnormal rates of urinary excretion of β_2-microglobulin, retinol binding protein, N-acetyl-β-glucosaminidase, ammo acids, and calcium in individuals with cadmium excretion rates >2 μg/day (Buchet et al. 1990). The cadmium excretion rate of 2 μg/day was estimated to correspond to a cadmium level of 50 μg/g wet weight in the renal cortex (Buchet et al. 1990). This study suggests that the critical concentration may be lower in members of the general population than in workers (Buchet et al. 1990). However, data from Japanese residents of cadmium-polluted areas support a critical concentration of 200 μg/g wet weight, as found in occupationally exposed workers (Roels et al. 1983). Quantitative analysis of the prevalence of elevated urinary β_2-microglobulin as a function of cadmium ingestion indicates that after a total intake of approximately 2,000 mg cadmium (for a 53-kg person), renal damage will occur (Nogawa et al. 1989). This intake corresponds to a 50-year dose of approximately 0.0021 mg/kg/day. A kinetic model of cadmium metabolism predicts that this intake will produce elevated β_2-microglobulin levels in about 5% of a nonsmoking European population (body weight=70 kg) and about twice that rate in a Japanese population (body weight=53 kg), assuming a log-normal distribution in critical concentrations with 10% of the population having a critical concentration of 180 μg/g or less and 50% having a critical concentration at 250 μg/g or less (Kjellstrom 1986a). This kinetic model also assumes that kidney concentrations will be log-normally distributed in a population with a given intake (Kjellstrom

1986a); it has been suggested that the standard deviation for this distribution is 1.75 rather than 2, and that intakes to produce a given probability of renal effects are 50% higher than predicted by the model (Piscator 1985). Possible reasons for the discrepancy of the model with the Buchet et al. (1990) study, but agreement with the Nogawa et al. (1989) study, include differences in the cutoffs for elevated β_2-microglobulinuria and differences in estimation of dietary cadmium absorption.

A chronic-duration oral MRL has been derived from the NOAEL of 0.0021 mg/kg/day in the Nogawa et al. (1989) study. The MRL is 0.0002 mg/kg/day, using an uncertainty factor of 10 to account for sensitive members of the population (see the footnote to Table 2-2 and Appendix A). The chronic-duration oral MRL is shown in Figure 2-2.

Proteinuria does not decrease when oral exposure to cadmium stops. Renal tubular dysfunction and reduced glomerular filtration increase in severity after cessation of environmental exposure (Iwata et al. 1993; Kido et al. 1990b). Although kidney failure is not the primary cause of death among populations environmentally exposed to cadmium, increased rates of mortality from renal disease have been observed in populations of Belgium (Lauwerys and De Wals 198l), England (Inskip and Beral 1982) (although not significant), and Japan (Nakagawa et al. 1987) (significant for females and not significant for males). The increased calcium excretion associated with cadmium-induced renal damage may also increase the risk for osteoporosis, particularly in post-menopausal women (Buchet et al. 1990).

In two fatal cases of oral cadmium poisoning, anuria was present in one individual who ingested 25 mg/kg cadmium as cadmium iodide. Damage to the kidneys was reported at autopsy but was not further specified (Wisniewska-Knypl et al. 1971). The kidneys were reported as normal at autopsy in an individual who died 2 days after ingesting 1,840 mg/kg cadmium (Buckler et al. 1986).

Numerous studies in rats, mice, and rabbits confirm that oral exposure to cadmium causes kidney damage including proteinuria and tubular damage (Andersen et al. 1988; Bernard et al. 1980, 1988a, 1992; Bomhard et al. 1984; Borzelleca et al. 1989; Cardenas et al. 1992a, 1992b; Cha 1987; Fingerle et al. 1982; Gatta et al. 1989; Gill et al. 1989b; Itokawa et al. 1974; Kawamura et al. 1978; Kotsonis and Klaassen 1978; Kozlowska et al. 1993; Mangler et al. 1988; Masaoka et al. 1994; Pleasants et al. 1992, 1993; Prigge 1978a; Steibert et al. 1984; Stowe et al. 1972; Wilson et al. 1941). Histopathological findings include focal necrosis of proximal tubular epithelial cells and cloudy swelling in renal tubules (Cha 1987).

Some studies have also shown no effect on renal function (Basinger et al. 1988; Borzelleca et al. 1989; Boscolo and Carmignani 1986; Groten et al. 1990; Jamall et al. 1989; Loeser and Lorke 1977a, 1977b).

In acute-duration gavage studies in rats, decreased urine flow (Kotsonis and Klaassen 1977) and histopathologic evidence of kidney damage have been reported (Borzelleca et al. 1989) at the very high doses of 150 and 138 mg/kg/day, respectively. No effect on renal function was reported in rats receiving 13.9 mg/kg/day for 10 days in drinking water (Borzelleca et al. 1989). Mice treated with a single gavage dose showed tubular necrosis at 88.8 mg/kg in one study (Andersen et al. 1988), but no effects on the, kidney in another study at a dose of 112 mg/kg (Basinger 1988). Proteinuria is a common finding in intermediate-duration oral exposure studies in rats (Bernard et al. 1988a; Cardenas et al. 1992a, 1992b; Kotsonis and Klaassen 1978; Prigge 1978a), as are histopathologic changes in the kidney (Gatta et al. 1989; Itokawa et al. 1974; Kotsonis and Klaassen 1978; Wilson et al. 1941). Renal clearance was decreased in one study (Kawamura et al. 1978). Both increases (Pleasants et al. 1992, 1993) and decreases (Kozlowska et al. 1993) in relative kidney weight have been reported. These effects occurred in rats at doses ranging from 2 to 30 mg/kg/day. No renal effects were seen in dogs receiving 0.75 mg/kg/day cadmium for 3 months (Loeser and Lorke 1977b), but interstitial renal fibrosis was observed in rabbits exposed to 14.9 mg/kg/day for 200 days (Stowe et al. 1972). Renal dysfunction has been reported in rhesus monkeys exposed to 1.2 mg/kg/day for 9 years, but not at 0.4 mg/kg/day (Masaoka et al. 1994). Adverse renal effects are common in rats following chronic-duration oral exposure to cadmium. Proteinuria (Bernard et al. 1992; Bomhard et al. 1984) and histopathologic damage (Fingerle et al. 1982; Mangler 1988) have been reported at doses ranging from 1.8 to 12.5 mg/kg/day cadmium.

The hypothesis that a critical concentration of approximately 200 μg/g in the renal cortex must be reached before proteinuria develops is generally supported by the animal data (Bhattacharyya et al. 1988c; Kotsonis and Klaassen 1978; Manger et al. 1988; Shaikh et al. 1989; Viau et al. 1984).

Representative NOAEL and LOAEL values for kidney effects for each species and duration category, expressed as ingested dose, are recorded in Table 2-2 and plotted in Figure 2-2.

Endocrine Effects. No studies were located regarding endocrine effects in humans after oral exposure to cadmium.

Evidence for endocrine effects in animals after oral exposure to cadmium is limited to histopathologic examination of endocrine tissues. No adverse effects were seen in parathyroid glands from female Wistar rats exposed to 8 mg Cd/kg/day via drinking water for 90 days (Kawamura et al. 1978) or in adrenal gland from male Sprague-Dawley rats exposed to 8 mg/kg/day via drinking water for 24 weeks (Kotsonis and Klaassen 1978). Pituitary, adrenals, thyroid and thymus were unaffected in Wistar rats exposed to 3 mg/kg/day cadmium via feed for 3 months (Loeser and Lorke 1977a). Wilson et al. (1941) reported pancreatic atrophy and pancreatitis in rats from cadmium at 2.79 mg/kg/day via feed for 100 days. In rabbits exposed to 14.9 mg Cd/kg body weight/day via drinking water for 200 days the pancreas had moderate concentrations of cadmium, but no interstitial fibrosis or other pathologic alterations (Stowe et al. 1972).

Dermal Effects. No studies were located regarding dermal effects in humans after oral exposure to cadmium.

Coarse fur was reported in Long-Evans rats receiving 6.13 mg/kg/day cadmium during Gd 6-15 (Machemer and Lorke 1981). A ruffled hair coat was reported in Wistar rats receiving 40 mg/kg/day cadmium by gavage 5 days a week for 14 weeks (Baranski and Sitarek 1987). No other reports of dermal effects after oral exposure to cadmium were located.

Ocular Effects. No studies were located regarding ocular effects in humans or animals after oral exposure to cadmium.

Body Weight Effects. No studies were located regarding body weight effects in humans after oral exposure to cadmium were located.

Decreased body weight and decreased rates of growth are common findings in studies where experimental animals are orally exposed to cadmium. Sprague-Dawley rats receiving a single gavage dose of 150 mg/kg cadmium exhibited a 12% decrease in body weight, but 100 mg/kg had no effect (Kotsonis and Klaassen 1977). Daily gavage doses of 15.3 mg/kg over a 10-day period caused a 79% decrease in body weight gain in male Sprague-Dawley rats (Borzelleca et al. 1989). Significant reductions in maternal weight gain have also been reported (Baranski 1985; Machemer and Lorke 1981).

Body weight reductions are also seen in intermediate-duration studies. For example, in a 14-week exposure via drinking water in male Long-Evans rats, 2.9 mg/kg/day had no effect on body weight gain; however, 5.8 mg/kg/day caused a 6-23% decrease and 11.6 mg/kg/day caused a 47-58% decrease (Pleasants et al. 1992, 1993). In general, intermediate-duration doses in feed or drinking water of 3 mg/kg/day or less have either no effect or only a small effect (10-20% decrease) on body weight in rats (Carmignani and Boscolo 1984; Jamall et al. 1989; Loeser and Lorke 1977a; Muller et al. 1988; Ogoshi et al. 1989; Perry et al. 1989; Wilson et al. 1941). Higher doses (4-14 mg/kg/day) had no effect in some studies (Kostial et al. 1993; Kotsonis and Klaassen 1978; Prigge 1978a; Viau et al. 1984) and small effects in others (Cha 1987; Kawamura et al. 1978; Kozlowska et al. 1993). A 29% decrease in maternal weight gain was observed in rats exposed to a high dose of 40 mg/kg/day (Baranski and Sitarek 1987). In mice, a dose of 4.8 mg/kg/day had no effect on maternal weight gain, but a dose of 9.6 mg/kg/day caused a 14% decrease (Webster et al. 1978). A high dose of 232 mg/kg/day in mice caused a 29% decrease in body weight (Waalkes et al. 1993). Beagle dogs were unaffected at 0.75 mg/kg/day (Loeser and Lorke 1977b), as were rabbits at up to 2.2 mg/kg/day (Boscolo and Carmignani 1986; Tomera and Harakai 1988). A small decrease (11%) was seen in rabbits exposed to 14.9 mg/kg/day for 200 days (Stowe et al. 1972).

A chronic-duration study in rhesus monkeys reported decreased growth rates at 0.4 mg/kg/day, but no effect at 0.12 mg/kg/day (Masaoka et al. 1994). No effect on body weight was seen in rats at up to 4.4 mg/kg/day (Decker et al. 1958; Fingerle et al. 1982; Mangler 1988), but a small effect was seen at 7 mg/kg/day (Waalkes and Rehm 1992). Decreased terminal body weight was observed in mice after 12 months of drinking-water exposure to a high dose of 57 mg/kg/day (Hays and Margaretten 1985).

Metabolic Effects. Hyperthermia and metabolic acidosis were reported in a human male who had ingested 25 mg/kg cadmium as cadmium iodide (Wisniewska-Knypl et al. 1971).

No studies were located regarding metabolic effects in animals after oral exposure to cadmium.

2.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans after oral exposure to cadmium.

Numerous studies in rats, mice, and monkeys have established the capability of cadmium to affect the immune system, but the clinical significance of the effects is not clear. In mice, intermediate-duration oral exposure to cadmium has been shown to increase resistance to viral infection (Exon et al. 1986), to be without effect on natural or acquired resistance to infection (Bouley et al. 1984), and to increase mortality

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2.2.2.4 Neurological Effects

A few studies have reported an association between environmental cadmium exposure and neuropsychological functioning. These studies used hair cadmium as an index of exposure (see Section 2.7.1 for a discussion of the limitations of using hair as an indicator of exposure). End points that were affected included verbal IQ in rural Maryland children (Thatcher et al. 1982), acting-out and distractibility in rural Wyoming children (Marlowe et al. 1985), and disruptive behavior in Navy recruits (Struempler et al. 1985). The usefulness of the data from these studies is limited because of the potential confounding effects of lead exposure; lack of control for other possible confounders including home environment, caregiving, and parental IQ levels; and an inadequate quantification of cadmium exposure.

Although a cadmium induced neurotoxicity has not been clearly demonstrated in human studies, it has been observed in animal studies. Both a single oral exposure (Kotsonis and Klaassen 1977) and intermediate duration exposure of adult rats to cadmium resulted in significantly decreased motor activity (Kotsonis and

Klaassen 1978; Nation et al. 1990). Intermediate-duration oral exposure to cadmium has also been reported to cause weakness and muscle atrophy (Sato et al. 1978), induce aggressive behavior (Baranski and Sitarek 1987), induce anxiety as manifested by increased passive avoidance behavior (Nation et al. 1984) and by increased ethanol consumption (Nation et al. 1989), and alter brain biogenic amine content and enzyme activities (Murthy et al. 1989). Doses associated with these effects range from 5 to 40 mg/kg/day cadmium. Degenerative changes in the choroid plexus have been reported in mice exposed to 1.4 mg/kg/day cadmium in drinking water for 22 weeks (Valois and Webster 1989). Peripheral neuropathy has been reported in rats after a 31-month exposure to cadmium in drinking water (Sato et al. 1978). Neurological effects in offspring of animals orally exposed to cadmium during gestation are discussed in Section 2.2.2.5. Representative NOAEL and LOAEL values for neurological effects of oral cadmium exposure in each species and duration category are reported in Table 2-2 and plotted in Figure 2-2.

2.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in men or women after oral exposure to cadmium.

A number of animal studies have shown adverse reproductive effects to male and female reproductive capacity from cadmium exposure. In male rats and mice, acute oral exposure to near-lethal (60-100 mg/kg) doses can cause testicular atrophy and necrosis (Andersen et al. 1988; Bomhard et al. 1987; Borzelleca et al. 1989), and concomitant decreased fertility (Kotsonis and Klaassen 1978). Lower-dose acute exposures of 25-50 mg/kg did not result in reproductive toxicity in male animals (Andersen et al. 1988; Bon-hard et al. 1987; Dixon et al. 1976).

The following intermediate-duration dosing regimens resulted in neither testicular histopathologic lesions nor a decrease in male reproductive success: 0.25 mg Cd/kg/day via gavage for 10 weeks (Bomhard et al. 1987); 5 mg/kg/day via water for 30-90 days (Dixon et al. 1976); 2.5 mg/kg/day via food for 4 weeks (Groten et al. 1990); 8 mg/kg/day via water for 24 weeks (Kotsonis and Klaassen 1978); 3 mg/kg/day via food for 12 weeks (Loeser and Lorke 1977a, 1977b); 2.9 mg/kg/day via water for 14 weeks (Pleasants et al. 1992); and 4.64 mg/kg/day via water for 70-80 days (Zenick et al. 1982). Some dosing regimens have resulted in adverse reproductive effects. Male rats exposed to 8.58 mg Cd/kg/day in water for 10 weeks developed necrosis and atrophy of seminiferous tubule epithelium (Cha 1987). Rats exposed to 5.8 mg/kg/day via water for 14 weeks (Pleasants et al. 1992) or 11.6 mg/kg/day via water for 14 weeks (Pleasants et al. 1993) developed increased testes weight. Rats exposed to 12.9 mg/kg/day in water for 120 days developed significantly increased relative testis weight, decreased sperm count and motility,

decreased seminiferous tubular diameter, and seminiferous tubular damage (pyknotic nuclei, multinucleated giant cells, interstitial edema, and dilated blood vessels) (Saxena et al. 1989). In a protocol designed to assess the effects of vitamins on cadmium toxicity, Pleasants et al. (1992, 1993) reported that vitamins A and D_3 reduced the amount of cadmium-related increase in testis weight. Bomhard et al. (1987) reported no histopathologic lesions (other than those found in control animals as part of aging) in testes of rats receiving 10 weekly doses of 5 mg Cd/kg and followed for up to 30 months.

Higher doses of cadmium were generally needed to elicit a reproductive toxic response in females compared to the males. Although a dose of 65.6 mg Cd/kg/day via gavage for 10 days was sufficient to produce testicular atrophy and loss of spermatogenic element in male rats, no effects were seen in female rats up to 138 mg/kg/day (Borzelleca et al. 1989). Decreased percentage of fertilized females and percentage of pregnancies were reported at 61.32 mg Cd/kg/day via gavage for 10 days during gestation (Gd 6-15) (Machemer and Lorke 1981). No effect was seen at doses up to 18.39 mg/kg/day (Machemer and Lorke 1981). Baranski (1987) also reported no treatment related effects on number or percentage of females pregnant with 28.8 mg Cd/kg/day via gavage for 20 days during gestation (Gd l-20). Baranski and Sitarek (1987), however, administered 40 mg/kg by gavage 5 days a week for 14 weeks to female rats and observed a significant increased duration (twice as long) of the estrus cycle starting at 7-8 weeks and persisting to 14 weeks of exposure and the termination of the experiment. This adverse effect was not seen at 4 mg/kg (Baranski 1983; Baranski and Sitarek 1987).

Petering et al. (1979) exposed female rats to either 2.61 mg/kg/day via drinking water for 60 days prior to gestation or during gestation, or 5.23 mg/kg/day via drinking water for 111 days including 90 days prior gestation plus 21 days during gestation. These doses had no significant effects compared with controls for the number of pups stillborn. Pond and Walker (1975) also observed no effects in females from a cadmium exposure of 19.7 mg/kg/day via food for 21-25 days, including Gd 1 through lactation day (Ld) 1, on number of pups born. No effects from a cadmium exposure on number of pups born to females were observed for an exposure of 8.2 mg/kg/day via food for 15 days including Gd 6-20 (Sorell and Graziano 1990).

A dose of 10 mg Cd/kg/day once a day via gavage for 9 weeks (6 weeks prior to gestation and 3 weeks of gestation) significantly decreased the number of copulating and pregnant females, and the number of implants and live fetuses (Sutou et al. 1980). No effect was seen at 1 mg/kg/day (Sutou et al. 1980).

Reproductive effects on both male and female rats orally exposed to 2.5 mg/kg/day via drinking water for 180 days may have resulted in the observed decrease in litter size and increased interval between litters. Both males and females were treated over two generations. Three of five pairs failed to breed in the second generations (Schroeder and Mitchener 1971). No histopathologic lesions were found in testes or uteri of dogs given $CdCl_2$ at 0.75 mg/kg/day via food for 3 months (Loeser and Lorke 1977b).

Male rats were exposed to 0-14 mg Cd/kg/day via food for 77 weeks. The incidence of prostatic hyperplasias was increased above controls (1.8%) from the 3.5 mg Cd/kg/day dose. The overall incidence for prostatic lesions for all cadmium-treated groups was much lower in zinc-deficient rats, possibly because of a marked increase in prostatic atrophy that was associated with reduced zinc intake. Moreover, there was not a clear dose-response increase in prostatic proliferative lesions. Testicular tumors (exclusively benign interstitial tumors) increased significantly only at the highest-dose cadmium with diets adequate in zinc. Male Wistar rats exposed to cadmium in the drinking water at 0, 25, 50, 100, or 200 ppm developed tumors of the prostate (50 ppm), testes (200 ppm), and hematopoietic system (50 ppm), while dietary zinc deficiency has complex, apparently inhibitory effects on cadmium carcinogenesis by this route (Waalkes and Rehm 1992).

Red-white Meuse-Rhine-Yssel (MRY) dairy cows from two cohorts in Kempenland, Holland, were studied to detect reproductive effects of cadmium by using an historical data set. Data on accumulated exposure to cadmium had been recorded at slaughter over a 3-year period for cows in the 2 cohorts. Each cow was registered for fertility characteristics (decreased fertility, increased fetal death, increased complications at birth, and decreased twinning rate) and milk production; birth defects and body weights were not recorded. Cadmium content in the kidney was 2.5 times higher in the exposed cohort when compared to the unexposed. The cohort used as a control group (N=24) came from an area with cadmium ground water levels of 0.1 μg/L and cadmium soil levels of 0.4 mg/kg/dry weight. The exposed cohort (N=89) came from an area with cadmium ground water levels of 0.1-25 g/L and cadmium soil levels of 1-2.5 mg/kg/day weight. Two-sided 95% confidence intervals were calculated for all odds ratios derived from logistic regression and rate ratios resulting from the Cox proportional hazards model. A significantly increased number of inseminations were required for conception in cows from the exposed area, although the incidence of longer intervals between inseminations was not increased. Significantly fewer twins were born to cows from the exposed area and death among twins was increased (non-significantly). No increased intra-uterine death was observed in cows from the exposed area. The number of cows slaughtered for

reasons possibly related to cadmium (perinatal death and premature death) was not increased (Kreis et al. 1993).

Representative NOAEL and LOAEL values for reproductive effects in each species and duration category are reported in Table 2-2 and plotted in Figure 2-2.

2.2.2.6 Developmental Effects

There are very limited data on the developmental effects of cadmium in humans. Urinary cadmium content was measured in women three days after giving birth and compared to smoking habits and birth weight of offspring. Among nonsmoking women, when cadmium content was expressed as μg/L, cadmium levels were higher in women with infants of below-normal birth weight. However, when cadmium content was expressed as μg/g creatinine, cadmium levels were lower in women with infants with below-normal birth weight. Cadmium levels in smoking women were lower in both μg/L and μg/g in women with infants with below-normal birth weight (Cresta et al. 1989).

Cadmium and lead content in hair of rural French women and their newborns related to parity, birth weight, and maternal hypertension. The cadmium content was slightly higher in the newborns' hair when compared to their mothers' hair. A positive association for cadmium content was found between newborn and mother (i.e., placental transfer). Cadmium levels in the hair of newborns of hypertensive mothers were 3 times as high as in the hypertensive mothers themselves (Hue1 et al. 1981). No other studies were located regarding developmental effects in humans after oral exposure to cadmium.

A number of studies in rats and mice indicate that cadmium can be fetotoxic from oral exposures prior to and during gestation. This fetotoxicity is most often manifested as reduced fetal or pup weights (Ali et al. 1986; Baranski 1987; Gupta et al. 1993; Kelman et al. 1978; Kostial et al. 1993; Petering et al. 1979; Pond and Walker 1975; Sore11 and Graziano 1990; Sutou et al. 1980; Webster 1978; Whelton et al. 1988), but malformations, primarily of the skeleton, have been found in some studies (Baranski 1985; Machemer and Lorke 1981; Schroeder and Mitchener 1971). Malformations or skeletal effects reported include sirenomelia (fused lower limbs), amelia (absence of one or more limbs), and delayed ossification of the sternum and ribs (Baranski 1985); dysplasia of facial bones and rear limbs, edema, exenteration, cryptorchism, and palatoschisis (Machemer and Lorke 1981); and sharp angulation of the distal third of the tail (Schroeder and Mitchener 1971). Dosing levels were in the l-20 mg/kg/day range.

The most sensitive indicator of developmental toxicity of cadmium in animals appears to be neuro-behavioral development. Offspring of female rats orally exposed to cadmium at a dose of 0.04 mg/kg/day prior to and during gestation had reduced exploratory locomotor activity and rotorod performance at age 2 months (Baranski et al. 1983). Pups from dams exposed to 0.7 mg/kg/day during gestation had significant delays in cliff aversion and swimming behavior. Locomotor activity was significantly increased In post-weaning measurements, locomotor activity was significantly decreased in treated groups at 60 days of age; conditioned avoidance behavior was also significantly decreased when tested at 60 and 90 days of age (Ali et al. 1986).

Nagymajtenyi et al. (1997) also reported behavioral and functional neurotoxicological changes caused by cadmium in a three-generational study in rats. Three consecutive generations of Wistar rats were orally treated by gavage with 3.5, 7.0, or 14.0 mg Cd/kg bw (as cadmium chloride diluted in distilled water) over the period of pregnancy, lactation, and 8 weeks after weaning. Behavioral (open field behavior) and electrophysiological (spontaneous and evoked cortical activity, etc.) parameters of male rats from each generation were investigated at the age of 12 weeks. The main behavioral outcomes were increased vertical exploration activity (rearing) and increased exploration of an open-field center. The spontaneous and evoked electrophysiological variables showed dose- and generation-dependent changes (increased frequencies in the electrocorticogram, lengthened latency and duration of evoked potentials, etc.) signaling a change in neural functions. The results indicate that low-level, multigeneration exposure of rats to inorganic cadmium can affect nervous system function.

Desi et al. (1998) continued the above studies to further evaluate cadmium associated changes in behavior and neurological function in rats following different dosage regimens during pregnancy. Female Wistar rats were given 3.5, 7.0, or 14.0 mg Cd/kg body weight (cadmium chloride dissolved in distilled water) in three different treatment regimes: days 5-15 of pregnancy; days 5-15 of pregnancy + 4 weeks of lactation; and days 5-15 of pregnancy + 4 weeks of lactation followed by the same oral treatment of male rats of the Fl generation for 8 weeks. The behavioral (open-field exploration) and electrophysiological (electrocortico gram, cortical-evoked potentials, conduction velocity and refractory periods of a peripheral nerve) parameters of Fl male rats exposed by various treatments were investigated at the age of 12 weeks. The results indicate that cadmium altered the spontaneous and evoked electrophysiological functions (e.g., increased the frequency of the electrocorticogram, lengthened the latency and duration of evoked potentials, etc.) in a dose and treatment time dependent manner. Only combining treatment during the prenatal development and the 4-week suckling period resulted in a significant dose-dependent decrease of horizontal and vertical

exploratory activity and a significantly lower exploration frequency of the open-field center. The results suggests that low-level pre- and postnatal inorganic cadmium exposure affects the electrophysiological and higher order functions of the nervous system.

A study by Gupta et al. (1993) examined the developmental profiles of DNA, RNA, proteins, DNA synthesis, thymidine kinase activity, and concentrations of zinc and cadmium in the brain of neonates from dams exposed to cadmium acetate at 5-6.3 mg/kg/day in drinking water during gestation, and 7-8 mg/kg/day during a 21-day lactation period. Pup brain and body weights were significantly decreased in the cadmium exposed pups on Ld 7-21. Cadmium brain accumulation was significantly increased in exposed pups on Ld 7 and remained at similar levels on Ld 14 and 21. DNA and thymidine kinase brain levels were significantly decreased in treated pups compared with controls on Ld 7, 14, and 21. The toxicological significance of changes in DNA incorporation and thymidine kinase activity are uncertain.

Xu et al. (1993b) determined lipid peroxide (LPO) concentrations in rat pups in various organs as an index of cadmium toxicity. Male and female Wistar mice were exposed to cadmium in drinking water at 0, 5.7, or 14.25 mg/kg/day for 2 months prior to mating. The pregnant females continued to be exposed during gestation and lactation. Litter size and pup survival rates were unaffected by cadmium. Body weights were not statistically different between the exposed and control groups. In pups, brain weights (at 5.7 and 14.25 mg/kg/day) and liver, kidney, and heart weights (at 14.25 mg/kg/day) were significantly decreased. Although the relative organ weights were lower in the high-dose group, the difference from controls was not statistically significant. LPO concentrations in all organs were significantly increased in pups on Ld 7 at 14.25 mg/kg/day except in the kidney; concentrations in the liver, heart, and brain were 131.5, 156, and 237.4%, respectively, of the concentrations in controls.

In contrast to most of the study results, Saxena et al. (1986) reported no developmental effects from an exposure to 21 mg Cd/kg/day via drinking water during gestation (Gd 0-20). This study evaluated simultaneous exposure to lindane (20 mg lindane/kg via gavage on Gd 6-14) and cadmium acetate in drinking water at doses that individually did not cause maternal or developmental effects. Maternal toxicity (significantly decreased weight gain) and developmental toxicity were only observed in the cadmium plus lindane group. Fetal body weight was significantly decreased; intrauterine death and the rate of skeletal anomalies were significantly increased. Anomalies consisted of decreased ossification, wavy ribs, and scrambled sternebrae.

Representative NOAEL and LOAEL values for developmental effects in animals from oral exposure to cadmium for acute and intermediate durations are listed in Table 2-2 and plotted in Figure 2-2.

2.2.2.7 Genotoxic Effects

There are mixed results on the genotoxicity of oral cadmium exposure. Examination of lymphocytes from women environmentally exposed to cadmium (Itai-Itai patients) have shown statistically significant increases in chromosomal aberrations in one study (Shiraishi and Yoshida 1972), but these results were not replicated in another study (Bui et al. 1975). A recent study of inhabitants of a cadmium-polluted area of China found an increase in chromosomal aberrations that was correlated with urinary cadmium level (Tang et al. 1990).

No abnormalities of bone marrow were found in mice exposed to cadmium at 600 ppm in the diet for 1 month (Deknudt and Gerber 1979), but bone marrow abnormalities were found in mice after 1 week at 3.52 mg/kg/daily in a dosing regimen of cadmium by daily gavage for l-3 weeks with a dose range from 1.76-17.6 mg/kg (Mukherjee et al. 1988b). No evidence for germ cell mutations in male rats orally exposed to cadmium (the dominant lethal test) has been found (Sutou et al. 1980; Zenick et al. 1982). Other genotoxicity studies are discussed in Section 2.5.

2.2.2.8 Cancer

A few studies of cancer rates among humans orally exposed to cadmium have been performed. No significant increase in cancer rates was found among residents of a cadmium-polluted village in England (Inskip and Beral 1982) or in prostate, kidney, or urinary tract cancer among residents of a cadmium polluted area of Belgium (Lauwerys and De Wals 1981). The geographic distribution of elevated rates of prostate cancer incidence was shown to parallel the distribution of elevated cadmium concentrations in water, soil, or grain crops in Alberta, Canada (Bako et al. 1982). In none of these three studies were estimates made of cadmium exposures of populations as a whole or of individuals with cancer. A retrospective mortality study was done for three areas of Japan classified on the basis of rice Cd-content as highly polluted, slightly polluted, or non-polluted. No significant differences were found in mortality from cancer of all sites including prostate cancer (Shigematsu 1984).

One study examined cadmium, zinc, and copper in human kidney tumors and normal kidneys. Kidneys with renal cell carcinoma in cortex from 31 cases (20 men and 11 women) were compared to kidneys of patients who had died from causes other than a malignant disease from 17 controls (9 men and 8 women). No one in this study had been occupationally exposed. Smoking habits for patients were recorded. The level of cadmium in tumor tissue did not correlate with cadmium in cortex or medulla in the same kidney. No significant difference was found between cases and controls; although smoking cases had higher levels of cadmium. It was concluded that cadmium was not a risk factor for renal cell carcinoma (Hardell et al. 1994).

Inhabitants of cadmium-polluted areas of Japan with elevated urinary retinol binding protein excretion had a mortality rate from malignant neoplasms no different from expected (Nakagawa et al. 1987). Overall, there is little evidence of an association between oral exposure to cadmium and increased cancer rates in humans, but the statistical power of the available studies to detect an effect was not high.

In rats and mice, earlier studies on chronic oral exposure to cadmium have not reported an increased overall cancer incidence or the incidence of specific tumor types (Kanisawa and Schroeder 1969; Levy and Clack 1975; Levy et al. 1975; Loser 1980; Mangler et al. 1988; Schroeder et al. 1964, 1965). However, maximum daily doses tested were only 1 mg/kg/day in mice (Schroeder et al. 1964) and 3.5 mg/kg/day in rats (Loser 1980) and, in most of these studies, histopathologic examination was limited compared to contemporary standards. Loser (1980) did perform a relatively thorough histological examination. A few additional animal studies of noncancer effects of chronic-duration oral cadmium exposure have indicated that no dose-related increases in tumors were found at maximum doses of 4.01 mg/kg/day in rats (Fingerle et al. 1982) or 8 mg/kg/day in mice (Watanabe et al. 1986).

More recently, Waalkes and Rehm (1992) evaluated the effects of chronic dietary zinc deficiency on oral cadmium carcinogenesis in male Wistar rats. Rats were exposed to cadmium at 0, 25, 50, 100, or 200 ppm with adequate (60 ppm) zinc or deficient zinc (7 ppm) in the diet for 77 weeks. A complete necropsy was performed on all animals. Survival rate and food consumption were not affected in this study. The incidence of prostatic proliferative lesions, both hyperplasias and adenomas, was increased above controls (1.8%) in both zinc adequate (20%) and zinc deficient (14%) rats fed 50 ppm cadmium. The overall incidence for prostatic lesions for all cadmium-treated groups was much lower in zinc-deficient rats, possibly because of a marked increase in prostatic atrophy that was associated with reduced zinc intake. Moreover, there was not a clear dose-response increase in prostatic proliferative lesions. Cadmium

treatment resulted in an elevated leukemia incidence (large granular lymphocytes; maximum 4.8-fold over control) in both zinc-adequate and zinc-deficient groups. A significant increase in the incidence of leukemia in the zinc-adequate diet was seen at 50 and 100 ppm cadmium, but not at 200 ppm. Zinc deficiency reduced the potency of cadmium (i.e., higher doses needed for comparable incidence). There was a consistent increase in the incidence of leukemia with an increasing cadmium dose in the zinc-deficient group, but the increase was statistically significant only at 200 ppm. The highest incidence of leukemia observed from cadmium (28%), however, was seen in the 200 ppm zinc-deficient rats. Testicular tumors (exclusively benign interstitial tumors) increased significantly only at 200 ppm cadmium with diets adequate in zinc. A significant positive trend was noted for development of testicular neoplasia with increased cadmium dose. Thus, oral cadmium exposure, in this study, was associated with tumors of the prostate, testes, and hematopoietic system in rats, while dietary zinc deficiency has complex, apparently inhibitory, effects on cadmium carcinogenesis by this route.

A subsequent study by Waalkes et al. (1993) using male B6C3F$_1$ mice evaluated the effects of cadmium exposure on tumor incidence at various times after the initiation of the carcinogenic process. The possible role of metallothionein in the susceptibility of transformed cells to cadmium cytotoxicity was also evaluated. At 5 weeks of age, mice received an intraperitoneal injection of N-nitrosodiethylamine (NDEA) at 90 mg/kg. At 2, 4, 8, 16, or 32 weeks post-NDEA injection, mice received water containing 1,000 ppm cadmium *ad libitum* for up to 48 weeks of post-NDEA exposure. Cadmium exposure caused a marked “reduction” in liver tumor incidence in NDEA treated mice even when given as late as 32 weeks after the initial NDEA treatment. Cadmium alone eliminated the spontaneously occurring incidence of liver tumors (i.e., none out of 25 compared with 5 of 25 in the controls). Liver tumors produced by NDEA were typically basophilic adenomas. Cadmium resulted in a modest reduction in lung tumor incidence, statistically significant (28% reduction) only for the 16-48-week cadmium treated group pretreated with NDEA. Lung tumors were typically adenomas of alveolar cell origin. Cadmium alone eliminated spontaneously occurring lung tumors compared with the controls. Cadmium did significantly reduce the multiplicity of tumors induced by NDEA. NDEA alone typically induced 7 tumors per lung, while NDEA plus cadmium treatment reduced the number of tumors to 2.5-3.5 (data taken from a graph) with some cases showing an 80% reduction in tumor numbers. Lung tumors found in the cadmium plus NDEA treatment groups were also of a smaller overall size than those found in the NDEA-only treatment groups. Relatively little metallothionein was present in liver carcinomas,‘ liver adenomas, and lung adenomas as indicated by immunohistochemistry. This finding was confirmed biochemically for the liver tumors. The authors concluded that cadmium can effectively “impair” tumor formation in the lungs and liver of male

$B6C3F_1$ mice, and appears to be able to selectively destroy existing preneoplastic and/or tumor cells (adenomas). The mechanism may involve a reduced activity and responsiveness of the metallothionein system in transformed liver cells.

A 2-stage initiation/promotion experiment evaluated the promoting effects of cadmium chloride in the drinking water in rats. Cadmium exposure resulted in the following alterations in tumorigenic outcome: in the liver, hepatocellular carcinomas (initiated with diethyl nitrosamine) were decreased; in the stomach, tumors (initiated with N-methyl-*N*-nitro-nitrosoguanidine plus NaCl at 10% in the diet) were not affected; in the kidney, tumors (initiated with N-ethyl-*N*-hydroxyethyl nitrosamine) showed increased dysplastic foci but no increase in renal cell tumors; in the pancreas, tumors (initiated with *N*-nitroso-bis [2-oxopropyl] amine), had a nonsignificant increase in adenocarcinomas (female hamster study); and in the skin (initiated with 7,12-dimethyl benz(a)anthracene), there was no effect (female SENCAR mouse study) (Kurokawa et al. 1989).

Neither the human nor the animal studies provide sufficient evidence to determine whether or not cadmium is a carcinogen by the oral route.

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding death in humans after dermal exposure to cadmium.

Some guinea pigs died 2 or 6 weeks after being exposed in a skin depot (3.1 cm^2) to 2 mL of 0.239 molar aqueous of cadmium chloride (0.14 mg/kg body weight) (Wahlberg 1965). However, it is difficult to attribute these deaths to cadmium exposure, due to the low dose compared to oral LD_{50} values and to the fact that no necropsy was done to determine whether the exposed guinea pigs might have died from pneumonia (which killed some control guinea pigs) (Wahlberg 1965).

2.2.3.2 Systemic Effects

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

Dermal Effects. Among eczema patients routinely patch-tested with 2% cadmium chloride, 25 out of 1,502 showed some reaction (Wahlberg 1977). Since no reaction was found at lower dilutions in reactive patients (Wahlberg 1977), the effect was likely direct irritation of the skin and is indicated as a LOAEL value in Table 2-3.

No studies were located regarding dermal effects in animals after dermal exposure to cadmium.

Ocular Effects. No studies were located regarding ocular effects in humans after dermal exposure to cadmium.

Rats exposed to high concentrations of cadmium pigments or cadmium oxide in air had excessive lacrimation four hours after exposure (Rusch et al. 1986), possibly due to a direct irritation effect on the eyes.

2.2.3.3 Immunological and Lymphoreticular Effects

Dermal exposure to cadmium does not appear to affect the immune system significantly. One report of workers with extensive exposure to cadmium dust reported an increase in complaints of eczema (Friberg 1950); however, no subsequent studies have confirmed any association. Routine patch tests among dermatitis and eczema patients using up to 2% cadmium chloride solutions have found skin irritation at 2%, but no evidence of allergic reactions at a dose of 1% among people without known prior cadmium exposure (Rudzki et al. 1988; Wahlberg 1977) or among workers occupationally exposed to cadmium (Rudzki et al. 1988). Individuals with yellow tattoos containing cadmium sulfide often experience swelling of the surrounding skin on exposure to ultra violet (UV) irradiation (Bjornberg 1963); however, this may be the result of dermal damage from the photoconductivity of cadmium sulfide rather than a direct immunological reaction.

Table 2-3. Levels of Significant Exposure to Cadmium - Dermal

Species/ (Strain)	Exposure/ Duration/ Frequency	System	NOAEL	LOAEL				Reference Chemical Form
				Less Serious		Serious		
ACUTE EXPOSURE								
Systemic								
Human	once	Dermal	1%	2%	(skin irritation)			Wahlberg 1977 $CdCl_2$
Rat (Sprague-Dawley)	2 hr	Ocular				112 mg/m^3	(eyes closed from exposure)	Rusch et al. 1986 CdO fume
Rat (Sprague-Dawley)	2 hr	Ocular		99 mg/m^3	(excessive lacrimation)			Rusch et al. 1986 CdS
Rat (Sprague-Dawley)	2 hr	Ocular		97 mg/m^3	(excessive lacrimation)			Rusch et al. 1986 CdSeS
Immunological/Lymphoreticular								
Human	once		1%					Rudzki et al. 1988 $CdCl_2$

hr = hour(s); LOAEL = lowest-observable-adverse-effect level; NOAEL = no-observable-adverse-effect level

Guinea pigs showed no contact sensitization following intradermal or topical exposure to cadmium chloride at concentrations up to 0.5% (Wahlberg and Boman 1979). NOAEL values for immunological effects in humans and guinea pigs after dermal cadmium exposure are shown in Table 2-3.

No studies were located regarding the following health effects in humans or animals after dermal exposure to cadmium:

2.2.3.4 Neurological Effects
2.2.3.5 Reproductive Effects
2.2.3.6 Developmental Effects
2.2.3.7 Genotoxic Effects

Other genotdxicity studies are discussed in Section 2.5,

2.2.3.8 Cancer

No studies were located regarding cancer in humans or animals after dermal exposure to cadmium.

2.3 TOXICOKINETICS

Cadmium metal and cadmium salts have low volatility and exist in air primarily as fine suspended particulate matter. When inhaled, some fraction of this particulate matter is deposited in the airways or the lungs, and the rest is exhaled. Large particles (greater than about 10 pm in diameter) tend to be deposited in the upper airway, while small particles (approximately 0.1 pm) tend to penetrate into the alveoli. Mucociliary clearance removes cadmium particles from the upper tract. Some soluble cadmium compounds (cadmium chloride and cadmium sulfate) may undergo limited absorption from particles deposited in the respiratory tree, but the major site of absorption is the alveoli. About one-quarter of the total inhaled cadmium is absorbed. Cadmium absorption from cigarettes appears to be higher than absorption from cadmium aerosols, probably due to the very small size of particles in cigarette smoke and the consequent very high alveolar deposition. The absorption of cadmium compounds from the lung does not always correlate with solubility as defined with water as the solvent. Little is known about the solubility of cadmium compounds in the biological fluids with the levels of CO_2 present in the lung.

Inhalation exposures primarily occur in the workplace. Most people in the general population are exposed to cadmium in the food or water. Most ingested cadmium passes through the gastrointestinal tract without being absorbed. Only about 5% of the total ingested cadmium (in food or water) is absorbed. The retention of cadmium in the gut slowly decreases over a period of 1-3 weeks. Absorption from the gut appears to take place in two phases, uptake from the lumen into mucosa, then transfer into the circulation. Factors affecting cadmium absorption include metal-metal (e.g., iron, calcium, chromium, magnesium, zinc) and metal-protein interactions (glutathione, sulfhydryl containing enzymes) in the body and in the food or water. Levels of other metals and proteins can vary with age and physiological status, and affect cadmium kinetics. Cadmium absorption is known to increase with iron or calcium deficiency, and increased fat in the diet (i.e., longer residency times for absorption to occur). Cadmium is not well absorbed by the skin (about 0.5%), and there is not a significant risk from skin exposure unless contact with the skin is for long periods of time or at very high levels.

Following absorption from any route of exposure, cadmium widely distributes throughout the body, with the major portion ending up in the liver and kidney. Average cadmium concentrations in the kidney are near zero at birth, and rise roughly linearly with age to a peak (typically around 40-50 μg/g wet weight) between ages 50 and 60, after which kidney concentrations plateau or decline. Liver cadmium concentrations also begin near zero at birth, increase to typical values of l-2 μg/g wet weight by age 20-25, then increase only slightly thereafter. Liver and kidney cadmium concentrations are comparable after short-term exposure, but the kidney concentration exceeds the liver concentration following prolonged exposure, except exposure to very high levels. Tissue distribution and retention of cadmium can differ significantly with age.

Most cadmium that is ingested or inhaled and transported to the gut via mucociliary clearance is excreted in the feces and is not absorbed into the body. Of the cadmium that is absorbed into the body, most is excreted very slowly, with urinary and fecal excretion being approximately equal. Half-times for cadmium in the whole body of mice, rats, rabbits, and monkeys have been calculated to be from several months up to several years. In the human body, the main portion of the cadmium body burden is found in the liver and kidney and in other tissues (particularly muscle, skin, and bone). Half-times for the human kidney have been estimated at between 6 and 38 years, and for the human liver at between 4 and 19 years. The placenta is only a partial barrier to fetal exposure to cadmium. Cadmium concentration has been found to be approximately half as high in cord blood as in maternal blood in several studies including both smoking and nonsmoking women. Cadmium can be excreted in human milk at levels from 5-10% of the levels in blood.

Cadmium is not known to undergo any direct metabolic conversion such as oxidation, reduction, or alkylation. The cadmium (+2) ion readily bind to anionic groups (especially sulfhydryl groups) in proteins (e.g., albumin and metallothionein) and other molecules. Of particular importance to the toxicokinetics of cadmium is its interaction with the protein metallothionein, a low-molecular-weight protein capable of binding as many as seven cadmium atoms per molecule. Metallothionein is inducible in most tissues by exposure to cadmium, zinc, and other metals, as well as organic compounds and a variety of other physiologic stresses (irradiation, food deprivation, exercise, hypothermia, and inflammation). The exact physiologic functions of metallothionein are not known. The interaction of cadmium with metallothionein may be related to the chemical similarities between cadmium and zinc. Initially cadmium in plasma circulates primarily bound to albumin. Cadmium enters the liver where it becomes bound to metallothionein and is released to the blood stream. Metallothionein-bound cadmium is readily filtered by the renal glomerulus and reabsorbed from the glomerular filtrate by the proximal tubule cells. The current hypothesis is that cadmium bound to exogenous metallothionein is degraded in tubular lysosomes releasing free cadmium that then induces synthesis of proximal tubular cell metallothionein. Renal damage is believed to occur if there is a localization of free cadmium or an excessive concentration of cadmium that remains unbound to metallothionein. Metallothionein metabolism in liver and kidney is relatively independent of the exposure route; inhalation exposure also induces metallothionein in the lung and oral exposure induces metallothionein in the intestine.

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

Cadmium metal and cadmium salts have low volatility and exist in air primarily as fine suspended particulate matter. When inhaled, some fraction of this particulate matter is deposited in the airways or the lungs, and the rest is exhaled. Large particles (greater than about 10 pm in diameter) tend to be deposited in the upper airway, while small particles (approximately 0.1 pm) tend to penetrate into the alveoli. While some soluble cadmium compounds (cadmium chloride and cadmium sulfate) may undergo limited absorption from particles deposited in the respiratory tree, the major site of absorption is the alveoli. Thus, particle size, which controls alveolar deposition, is a key determinant of cadmium absorption in the lung (Nordberg et al. 1985).

No direct data are available on cadmium deposition, retention, or absorption in the human lung. Data from animal studies indicate that lung retention is greatest after short-term exposure (5-20% after 15 minutes to 2 hours) (Barrett et al. 1947; Henderson et al. 1979; Moore et al. 1973; Rusch et al. 1986). The initial lung burden declines slowly after exposure ceases (Henderson et al. 1979; Moore et al. 1973; Rusch et al. 1986) due to absorption of cadmium and lung clearance of deposited particles. After longer periods of inhalation exposure to cadmium, somewhat lower lung retentions are found (Glaser et al. 1986). The absorption of cadmium in lung differs somewhat among chemical forms, but the pattern does not correlate with solubility (Glaser et al. 1986; Rusch et al. 1986).

Based on comparison of cadmium body burdens in human smokers and nonsmokers, cadmium absorption from cigarettes appears to be higher than absorption of cadmium aerosols measured in animals (Nordberg et al. 1985). The chemical form of cadmium in cigarette smoke is likely to be similar to that produced by other combustion processes, primarily cadmium oxide aerosols. The greater absorption of cadmium from cigarette smoke is likely due to the very small size of particles in cigarette smoke and the consequent very high alveolar deposition (Nordberg et al. 1985).

Based on the physiology of the human respiratory tree, a comprehensive model has been developed to predict the kinetics of inhaled cadmium in humans (Nordberg et al. 1985). Results of this model suggest that only about 5% of particles >10 μrn in diameter will be deposited, up to 50% of particles <0.1 μrn will be deposited, and between 50-100% of cadmium deposited in the alveoli will ultimately be absorbed (Nordberg et al. 1985).

2.3.1.2 Oral Exposure

Most ingested cadmium passes through the gastrointestinal tract without being absorbed (Kjellstrom et al. 1978). Measurement of gastrointestinal absorption is complicated by the fact that not all of a dose initially retained in the gastrointestinal system can be considered to be absorbed, because some portion may be trapped in the intestinal mucosa without crossing into the blood or lymph (Foulkes 1984). Thus, measures of whole-body cadmium retention may overestimate cadmium absorption (at least in the short-term). On the other hand, some absorbed cadmium may be excreted in urine or feces, so that retention may underestimate exposure. However, this underestimate is probably minor because excretion of absorbed cadmium is very slow (see Section 2.3.4.2).

The total retention of cadmium in the bodies of humans has been measured following ingestion of radioactive cadmium. About 25% of a dose of cadmium administered mixed with food to 5 healthy adults was retained after 3-5 days, but retention decreased to about 6% after about 20 days (Rahola et al. 1973). Similar results were obtained with 14 healthy adults, with an average of 4.6% of cadmium chloride in water taken with a meal retained in the body l-2 weeks after a simultaneously administered fecal marker (trivalent chromium) had been completely excreted (McLellan et al. 1978). The body store of iron influences cadmium absorption; subjects with low iron stores (assessed by serum ferritin levels) had an average absorption of 8.9%, while those with adequate iron stores had an average absorption of 2.3% (Flanagen et al. 1978). The influence of chemical complexation of cadmium on human absorption was evaluated in seven volunteers who ingested brown crab meat (hepatopancreas) that had been labeled with radioactive cadmium chloride by prior feeding of the crabs (Newton et al. 1984). Whole-body counting was used to evaluate uptake. Whole-body retention in the volunteers ranged from 1.2 to 7.6% with a mean of 2.7% (Newton et al. 1984), only slightly lower than the values of 4.6-6% obtained using dissolved cadmium ion (McLellan et al. 1978; Rahola et al. 1973). Comparisons of body burden of cadmium in nonsmokers with estimated daily intakes from the diet provide estimates of cadmium absorption from food of 3-5% (Ellis et al. 1979; Morgan and Sherlock 1984). These results indicated that, in general, cadmium absorption from food is not dependent on chemical complexation. However, some populations with high dietary-cadmium exposure from Bluff oysters (McKenzie-Parnell et al. 1988) or seal meat (Hansen et al. 1985) have been found not to have elevated blood-cadmium levels, perhaps due to the particular form of cadmium in these foods.

Most estimates of cadmium absorption in animals are somewhat lower than the values found from human studies, particularly after prolonged exposure. In mice, 0.5-3.2% of an oral dose of cadmium chloride was retained after 5 days (Engstrom and Nordberg 1979), and in rats, 2-3% of a single oral dose of cadmium chloride was retained (Moore et al. 1973; Schafer el al. 1990). Following 30 days of oral exposure, 0.2-0.3% of an administered dose was retained in rats (Muller et al. 1986). After 4 weeks of dietary exposure to cadmium, absorption of cadmium was reduced to one-third the absorption of unexposed rats (Schafer et al. 1990). After 35 days of exposure to cadmium chloride in drinking water, whole-body retention of cadmium was about 0.2% in female mice that had undergone pregnancy and lactation, but was only 0.08% in female mice that had not been pregnant (Bhattacharyya et al. 1986). Cadmium pigments (cadmium sulfide and cadmium sulfoselenide) appear to be absorbed much less than cadmium chloride in rats (ILZRO 1977).

The absorption of cadmium from the gastrointestinal tract has been extensively studied in rats and mice, and a number of factors are recognized that influence absorption. Absorption appears to take place in two phases: uptake from lumen into mucosa, and transfer into the circulation (Foulkes 1985). Phase 1 may involve sequestering of cadmium by metallothionein (Foulkes 1980), but any protective effect is overloaded at moderate doses (Kotsonis and Klaassen 1978). Uptake behaves like a saturable process with fractional absorption decreasing at high concentrations (Foulkes 1980). There is evidence, however, to suggest that this saturation results from charge neutralization at the membrane (Foulkes 1985), so that it need not be assumed that there is a specific system for carrying cadmium into the body. At doses high enough to damage gastrointestinal mucosa, fractional absorption is increased (Andersen et al. 1988; Goon and Klaassen 1989; Lehman and Klaassen 1986). Cadmium bound to metallothionein was absorbed by rats to a lesser extent than cadmium added to the diet as cadmium chloride, but kidney cadmium content was only slightly less (Groten et al. 1990).

Maitani et al. (1984) compared the distribution of cadmium after oral administration of either cadmium ions or Cd-thionein (Cd-TH) in male CF-1 mice given 0.5 mg Cd/kg, per os (po), as $CdCl_2$ in saline, $CdCl_2$ in control rat liver homogenate, Cd-TH in saline, Cd-TH in liver homogenate, or liver homogenate from Cd-treated rats. In all cases, 85-90% of the cadmium dose was present in feces within 24 hours. However, in groups receiving $CdCl_2$, more cadmium was found in feces on days 2 and 3, compared to those receiving Cd-TH. All treatments resulted in lower levels of cadmium in liver than in kidney. In a companion study, tissue levels indicated that less cadmium was absorbed when rats received Cd-TH in saline than $CdCl_2$ in saline. Cd-TH added to liver homogenate or liver homogenate containing Cd-TH increased the absorption of cadmium, resulting in renal cadmium levels similar to those in mice receiving $CdCl_2$ in saline. The kidney/liver cadmium concentration ratio (9) was the same for Cd-TH in all 3 media. Although Cd-TH gave much higher kidney/liver cadmium ratios than $CdCl_2$ (9 versus 2), renal cadmium concentrations were the same or lower than after $CdCl_2$ treatments. The authors concluded that the high kidney/liver cadmium ratio after Cd-TH treatment versus $CdCl_2$ was due to lower concentrations of cadmium in liver rather than marked increases in renal cadmium levels. While the chemical form of cadmium administered affects the absorption and distribution, the amount of cadmium reaching the kidney after Cd-TH administration is similar to that after $CdCl_2$ administration.

At moderate doses of cadmium, the presence of divalent and trivalent cations, such as calcium, chromium, magnesium, and zinc, may decrease cadmium uptake, probably by a nonspecific effect on the charge distribution of the intestinal brush border membrane (Foulkes 1985). However, the influence of cations on

cadmium absorption is complex, because zinc can increase the amount of cadmium absorbed from the intestine (Jaeger 1990). A refined diet high in fat and protein increases cadmium absorption in mice, partially due to increased gastrointestinal passage time (Schafer et al. 1986). Iron deficiency increases cadmium absorption (Flanagan et al. 1978; Schafer et al. 1990). Zinc deficiency may result in an increased accumulation of cadmium in the intestinal wall, but does not affect transport into the blood (Foulkes and Voner 1981; Hoadley and Cousins 1985). The absorption of cadmium in rats depends on age, with measured absorption decreasing from 12 to 5 to 0.5% at 2 hours, 24 hours, and 6 weeks after birth, respectively (Sasser and Jarboe 1977). Sasser and Jarboe (1980) also reported that absorption of cadmium in the gastrointestinal tract of young guinea pigs was 20-fold higher than in adult guinea pigs. Thus, for a given individual, the absorption following oral exposure to cadmium is likely to depend on physiologic status (age; body stores of iron, calcium, and zinc; pregnancy history; etc.) and, also, on the presence and levels of ions and other dietary components ingested with the cadmium.

2.3.1.3 Dermal Exposure

A few measurements of dermal absorption of cadmium in animals have been made, with only one *in vitro* study using human skin to determine the percutaneous absorption of cadmium.

A study by Wester et al. (1992) evaluated the percutaneous absorption of cadmium from water and soil into and through human skin using *in vitro* skin cells. Radioactive cadmium ($^{109}CdCl_2$) was made to a concentration of 116 ppb in water or 13 ppb in filtered soil (26% sand, 26% clay, 48% silt, 0.9% organic content). Cadmium chloride was administered either at 5 $\mu L/cm^2$ or 2 volumes of 2.5 $\mu L/cm^2$ (the same amount of cadmium apparently applied). Human cadaver skin derrnatomed at 500 pm was placed in flow through skin cells and perfused with human plasma. When an applied dose of $CdCl_2$ in water is applied to skin that is perfused for 16 hours, from 0.l- 0.6% enters the plasma perfusate over 16 hours, while 2.4-12.7% of applied dose remains in the skin. Most of the cadmium (74-93%) remained unabsorbed and was recovered from the skin surface. Total recoveries ranged from 88±20 to 103±3. No explanation was offered for the <100% recovery. When cadmium-contaminated soil (13 ppb $CdCl_2$) was applied to the skin surface, plasma levels ranged from 0.02 to 0.07% of the applied dose, while the skin contained 0.06-0.13% of applied dose. Surface wash ranged from 82 to 102% of applied dose. Total recoveries were from 83±33 to 106±2. The large differences between water and soil absorption into the plasma and retention in the skin were attributed to differences in cadmium partition coefficients, measured to be 3.61×10^1 for *stratum cormum* (powdered):water and 1.03×10^5 for soil:water. These measurements indicate that soil has

a relatively higher affinity for cadmium than does the stratum corneum. The transfer of cadmium from soil to skin depends on the soil's binding capacity and water retention and variables describing the physical contact with the skin. When cadmium levels in the soil were increased from 6.5 to 65 ppb, skin levels correspondingly increased, but plasma receptor fluid levels remained constant. This suggests that, with *in vitro* perfusion, the surface concentration of cadmium will influence skin cadmium concentration, but that absorption into plasma receptor fluid is relatively independent of the skin surface concentration. The authors offer the caveat that *in vitro* methods can influence results and so the receptor fluid accumulation must be interpreted with caution. The authors calculate that a whole body exposure to cadmium at 116 ppb in water with a 0.5% absorption will result in a daily systemic intake of about 10 μg cadmium.

A few animal studies are available that describe the percutaneous absorption of cadmium as estimated from the accumulation of cadmium in the liver and kidneys of mice and rabbits. One male rabbit (strain not specified) was dosed with $CdCl_2$ percutaneously with a 1% aqueous solution (6.1 mg Cd) or 2% ointment (12.2 mg Cd) over a 10 cm^2 shaved area. Animals were treated 5 times over 3 weeks. Only cadmium contents of liver and kidney were measured so total absorption through the skin may have been greater. Accumulated amounts of cadmium in the liver and kidneys were found to be 0.4-0.61% 2 weeks after the end of cadmium exposure. This percentage was similar for aqueous solution or hydrocarbon ointment. Similarly, one male hairless mouse (strain not specified) was dosed with $CdCl_2$ percutaneously with a 2% ointment (containing 0.61 mg Cd). Animals were treated 5 times over 3 weeks. Accumulated amounts of cadmium in the liver and kidneys were found to be 0.2-0.87%. Similarly, one male rabbit was dosed with $CdCl_2$ percutaneously with a 1% aqueous solution (6.1 mg Cd) or 2% ointment (12.2 mg Cd) over a 10 cm^2 shaved area. Animals were treated 5 times over 3 weeks. Accumulated amounts of cadmium in the liver and kidneys were found to be 0.4-0.61% 2 weeks after the end of cadmium exposure (Kimura and Otaki 1972).

Cadmium was detected in liver, kidneys, and urine following dermal exposure in guinea pigs (Skog and Wahlberg 1964). The disappearance of cadmium from cadmium chloride in water applied to guinea pig skin was dependent on concentration, with a peak mean absorption of 1.8% over 5 hours at 0.239 molar cadmium (about a 2.7% solution). Less absorption occurred at both at higher and lower concentrations of a cadmium chloride solution applied to the skin (Skog and Wahlberg 1964).

The results from all of these studies suggest that dermal absorption is slow, and would be of concern only in situations where concentrated solutions would be in contact with the skin for several hours or longer.

2.3.2 Distribution

Cadmium is widely distributed in the body, with the major portion of the body burden located in the liver and kidney. Animals and humans appear to have a similar pattern of distribution that is relatively independent of route of exposure, but somewhat dependent on duration of exposure.

2.3.2.1 Inhalation Exposure

Cadmium was found in autopsy samples from nearly all organs of a worker extensively exposed to cadmium dust, with greatest concentrations in the liver, kidney, pancreas, and vertebrae (Friberg 1950). In workers dying from inhalation of cadmium, lung-cadmium concentration is somewhat lower than liver or kidney cadmium concentration (Beton et al. 1966; Lucas et al. 1980; Patwardham and Finckh 1976). The concentration of cadmium in the liver of occupationally exposed workers generally increases in proportion to intensity and duration of exposure to values up to 100 μg/g (Gompertz et al. 1983; Roels et al. 1981b). The concentration of cadmium in the kidney rises more slowly than in the liver after exposure (Gompertz et al. 1983) and begins to decline after the onset of renal damage at a critical concentration of 160-285 μg/g (Roels et al. 1981b).

In animals acutely exposed to cadmium carbonate aerosols, about 60% of the inhaled dose is found in the gastrointestinal tract, transported by mucociliary clearance (Moore et al. 1973). Following a 2-hour inhalation of approximately 100 mg/m^3 of cadmium, cadmium concentration in rat liver increased from an initial concentration of 0.8 μg/g in males and 1.9 μg/g in females immediately after exposure up to a peak of about 2 μg/g in males and 3.8 μg/g in females 1 week postexposure, then declined to 1.7 and 2.5 μg/g, respectively, by 30 days postexposure. The kidney concentrations were initially <0.5 μg/g in males and females, rising to approximately 8 μg/g in both sexes by 1 week postexposure and to 18 μg/g in males and 15 μg/g in females by 30 days postexposure (Rusch et al. 1986).

2.3.2.2 Oral Exposure

As discussed in Chapter 5, most nonoccupationally exposed people are exposed to cadmium primarily through the diet. Cadmium can be detected in virtually all tissues in adults from industrialized countries, with greatest concentrations in the liver and kidney (Chung et al. 1986; Sumino et al. 1975). Average

cadmium concentrations in the kidney are near zero at birth, and rise roughly linearly with age to a peak (typically around 40-50 μg/g wet weight) between ages 50 and 60, after which kidney concentrations plateau or decline (Chung et al. 1986; Hammer et al. 1973; Lauwerys et al. 1984). Liver cadmium concentrations also begin near zero at birth, increase to typical values of l-2 μg/g wet weight by age 20-25, then increase only slightly thereafter (Chung et al. 1986; Hammer et al. 1973; Lauwerys et al. 1984; Sumino et al. 1975).

Distribution of cadmium in animals after oral exposure is similar to that found in humans, with highest accumulation in the liver and kidneys, and lower levels spread throughout the rest of the body (Kotsonis and Klaassen 1978; Weigel et al. 1984). Liver and kidney cadmium concentrations are comparable after short-term exposure (Andersen et al. 1988; Jonah and Bhattacharyya 1989), but the kidney concentration exceeds the liver concentration following prolonged exposure (Kotsonis and Klaassen 1978), except at very high exposures (Bernard et al. 1980).

Maitani et al. (1984) compared the distribution of cadmium in rats after an acute oral administration of either cadmium ions or cadmium bound to metallothionein. In all cases, 85-90% of the dose was present in the feces within 24 hours postexposure. More of the cadmium-thionein was retained after 2-3 days, and less of the cadmium-thionein was distributed to the liver than was the case for the ionic cadmium. Kidney levels were comparable.

Tissue distribution and retention of cadmium differed between 4-day-old rats and 70-day-old adults. Cadmium was 3-6 times more concentrated in the newborn spleen, bone, brain, testes, and muscle than in the adult rat 2 hours after an intravenous administration of 1 mg Cd/kg body weight. Liver concentration of metallothionein was 20 times greater in the newborn than in the adult; kidney metallothionein concentrations were comparable, but liver cadmium was only 30% higher and kidney cadmium 50% higher in the newborn. Nineteen days post-cadmium exposure, the retention of cadmium in the liver, kidney, and lung was similar in both the newborn and- the adult rat. The results indicate that metallothionein does not appear to play a major role in the tissue distribution or retention of cadmium (Wong and Klaassen 1980a).

The placenta may act as a partial barrier to fetal exposure to cadmium. Cadmium concentration has been found to be approximately half as high in cord blood as in maternal blood in several studies including both smoking and nonsmoking women (Kuhnert et al. 1982; Lauwerys et al. 1978; Truska et al. 1989). Accumulation of cadmium in the placenta at levels about 10 times higher than maternal blood cadmium

concentration has been found in studies of women in Belgium (Roels et al. 1978) and the United States (Kuhnert et al. 1982); however, in a recent study in Czechoslovakia, the concentration of cadmium in the placenta was found to be less than in either maternal or cord blood (Truska et al. 1989). In mice orally exposed to cadmium during pregnancy, maternal blood, placental, and fetal cadmium concentrations were essentially equal among control animals (with environmental cadmium exposure), but placental concentration increased with cadmium dose much more rapidly than either maternal blood or fetal cadmium concentration (Sorell and Graziano 1990). Thus, timing and level of cadmium exposure may influence the uptake of cadmium by the placenta, perhaps explaining the conflicting human studies.

Goyer et al. (1992) localized metallothionein in full-term human placenta and in fetal cells in human placenta. Metallothionein was present in trophoblasts (which facilitate transport of substances entering the placenta from the maternal blood), Hofbauer cells (motile macrophages capable of phagocytosis and protein ingestion), amniotic epithelial cells (fetal derivatives), and decidual cells (endometrial stromal cells that have been transformed under hormonal influence into large pale cells, rich in glycogen). The mechanism by which the placenta transports the essential metals, copper and zinc, while limiting the transport of cadmium is unknown, but may involve the approximately 1,000-fold higher concentration of zinc in the placenta and the higher affinity of cadmium than zinc for metallothionein.

Chan and Cherian (1992) report that pregnancy in Sprague-Dawley rats previously administered cadmium chloride (1.0 mg Cd/kg body weight subcutaneously, daily for 8 days) leads to a mobilization of cadmium from the liver (40% decrease compared to nonpregnant cadmium-treated controls) and an increase in the kidneys (60% increase). A similar pattern is seen for metallothionein. Plasma cadmium and metallothionein also increased in the pregnant group. Placental cadmium increased in the cadmium-treated rats compared to the untreated controls. In this rat model, then, pregnancy resulted in a transfer of hepatic cadmium and metallothionein via the blood to the kidney and placenta.

Cadmium levels in human milk are 5-10% of levels in blood, possibly due to inhibited transfer from blood because of metallothionein binding of cadmium in blood cells (Radisch et al. 1987).

2.3.2.3 Dermal Exposure

No studies were located regarding distribution in humans after dermal exposure to cadmium. Cadmium is found in the liver and kidneys of rats dermally exposed to cadmium, with higher accumulation in liver than kidney after 1 week and higher accumulation in kidney than liver after 3 weeks (Kimura and Otaki 1972).

2.3.3 Metabolism

Cadmium is not known to undergo any direct metabolic conversion such as oxidation, reduction, or alkylation. The cadmium (+2) ion does bind to anionic groups (especially sulfhydryl groups) in proteins (especially albumin and metallothionein) and other molecules (Nordberg et al. 1985). Plasma cadmium circulates primarily bound to metallothionein, and also to albumin and presumably other compounds as well (Foulkes and Blanck 1990; Roberts and Clark 1988).

Of particular importance to the toxicokinetics and toxicity of cadmium is its interaction with the protein metallothionein. Metallothionein is a low-molecular-weight protein, very rich in cysteine, which is capable of binding as many as seven cadmium atoms per molecule. Metallothionein is inducible in most tissues by exposure to cadmium, zinc, and other metals, as well as organic compounds and a variety of other physiologic stresses (irradiation, food deprivation, exercise, hypothermia, and inflammation) (Waalkes and Goering 1990). The exact physiologic functions of metallothionein are not known, and the interaction of cadmium with metallothionein may be related to the chemical similarities between cadmium and zinc (Waalkes and Goering 1990). Early work indicated that metallothionein binding decreased the toxicity of cadmium, and the ability of the liver to synthesize metallothionein appeared to be adequate to bind all the accumulated cadmium (Goyer et al. 1989; Kotsonis and Klaassen 1978).

More recently, Dorian et al. (1992a) evaluated the intra-renal distribution of ^{109}CdMT injected (intravenously) into male Swiss mice at a nonnephrotoxic dose (0.1 mg Cd/kg). Kidneys and liver were removed at 5, l 5, 30, 45, and 60 minutes; 2,4, 8, and 24 hours; and 2,4, and 7 days; and tissue concentration of cadmium determined. The radioactivity in the kidney reached a maximum level (85% of the dose) as early as 30 minutes following administration and remained essentially constant for up to 7 days after injection. Within the kidney, ^{109}Cd distributed almost entirely to the cortex. Light microscopic autoradio-graphy of the kidney showed that, within the cortex, ro9Cd distributed preferentially to the S1 and S2

segments of the proximal convoluted tubules. Within the S1 and S2 segments, the concentration of ^{109}Cd in the basal and apical parts of the cells was similar to that after the non-nephrotoxic dose of CdMT, but after a nephrotoxic dose (0.3 mg Cd/kg) the radioactivity distributed preferentially to the apical portion of the cells. In contrast, light microscopic autoradiography studies with $^{109}CdC1_2$ revealed that ^{109}Cd was more evenly distributed throughout the proximal tubules. After administration of a large dose of inorganic cadmium (3 mg Cd/kg), a similar concentration of cadmium was found in the convoluted and straight proximal tubules. The authors suggest that these date support the hypothesis that CdMT-induced nephrotoxicity might be due, at least in part, to its preferential uptake of CdMT into the S1 and S2 segments of the proximal tubules, the site of Cd-induced nephrotoxicity.

In a companion study, Dorian et al. (1992b) administered [^{35}S]CdMT intravenously to male Swiss at a nonnephrotoxic dose (0.1 mg Cd/kg), and evaluated the kidneys and liver at 5, 15, 30, 45, and 60 minutes; and 2, 4, 8, and 24 hours. The radioactivity in the kidney showed maximum level (80% of the dose) 15 minutes after the injection. This preferential renal uptake was also observed after administration of various doses of [^{35}S]CdMT. In contrast to the earlier observed persistency of ^{109}Cd in the kidney after ^{109}CdMT administration, ^{35}S disappeared rapidly (with a half-life of approximately 2 hours), and 24 hours after injection of [^{35}S]CdMT, there was very little ^{35}S left in the kidneys. These observations indicate that the protein portion of CdMT is rapidly degraded after renal uptake of CdMT and the released cadmium is retained in the kidney. Within the kidney, ^{35}S distributed mainly to the cortex. Light microscopic autoradiography showed that [^{35}S]CdMT preferentially distributed to the proximal convoluted tubule (S1 and S2), which is the site of nephrotoxicity. Within the S1 and S2 segments, a greater distribution of ^{35}S to the apical portion of the cells was observed after administration of both a non-nephrotoxic (0.1 mg Cd/kg) and a nephrotoxic (0.3 mg Cd/kg) dose. ^{109}Cd administered as ^{109}CdMT also distributed to the apical portion of the S1 and S2 cells. The results indicate that both the organic (^{35}S) and inorganic (^{109}Cd) portions of CdMT are rapidly and efficiently taken up by the S1 and S2 cells of the proximal tubules, the site of nephrotoxicity, and the protein portion is rapidly degraded to release cadmium.

The toxic effects and distribution of cadmium were compared after intravenous injection of ^{109}CdMT at 0.05 to 1 mg Cd/kg body weight and $^{109}CdC1_2$ at 0.1-3 mg/kg in male Swiss mice (Dorian et al. 1995). CdMT increased urinary excretion of glucose, and protein indicated renal injury with dosages as low as 0.2 mg Cd/kg. In contrast, renal function was unaltered by $CdCl_2$ administration, even at dosages as high as 3 mg Cd/kg. CdMT distributed almost exclusively to the kidney, whereas $CdCl_2$ preferentially distributed to the liver. However, a high concentration of cadmium was also found in the kidneys after

$CdCl_2$ administration (i.e., the renal cadmium concentration after administration of a high but non-nephrotoxic dose of $CdCl_2$ was equal to or higher than that obtained after injection of nephrotoxic doses of CdMT). Light microscopic autoradiography studies, using 0.3 mg Cd/kg as CdMT and 3 mg Cd/kg as $CdCl_2$, indicated that cadmium from CdMT preferentially distributed to the convoluted segments (S1 and S2) of the proximal tubules, whereas cadmium from $CdCl_2$ distributed equally to the various segments (convoluted and straight) of the proximal tubules. However, the concentration of cadmium at the site of nephrotoxicity, the proximal convoluted tubules, was higher after $CdCl_2$ than after CdMT administration. A higher cadmium concentration in both apical and basal parts of the proximal cells was found after $CdCl_2$ than after CdMT administration. The authors suggest that CdMT is nephrotoxic and $CdC1_2$ is not nephrotoxic because of a higher concentration of cadmium in the target cells after CdMT.

Because ZnMT and CdMT appeared to be handled by the same renal transport mechanism, the effects of ZnMT on ^{109}CdMT renal uptake and nephrotoxicity were evaluated (Dorian and Klaassen 1995). Swiss mice received a nephrotoxic intravenous dose of ^{109}CdMT (0.51 μmol MT/kg containing 0.4 mg Cd/kg,) or an equimolar dose of unlabeled ZnMT one minute before ^{l09}CdMT administration. Marked renal toxicity was observed 24 hours after ^{109}CdMT administration. In contrast, renal function appeared normal in mice receiving ZnMT before ^{l09}CdMT, although a similar concentration of ^{109}Cd was found in kidneys of both groups. The results indicate that ZnMT is not only nontoxic to the kidney at a dose as high as 5 μmole MT/kg, but it can also protect against the nephrotoxic effect of CdMT without decreasing renal cadmium concentration.

To further test the hypothesis that nephrotoxicity produced from chronic cadmium exposure results from a CdMT complex, Liu et al. (1998) exposed MT-null mice to a wide range of $CdCl_2$ doses, 6 times per week for up to 10 weeks. Renal cadmium burden increased with dose and duration up to 140 μg Cd/g kidney in control,mice (i.e., MT normal) with a 150-fold increase in renal metallothionein levels (800 μg MT/g kidney). Renal cadmium was much lower in MT-null mice (10 μg Cd/g) and MT levels were not detectable. The maximum tolerated dose of cadmium(as indicated by routine urinalysis and histopathology measures) in control mice was approximately 8 times higher than in MT-null mice. Lesions were more sever in MT-null mice than in controls, indicating that Cd-induced renal injury is not necessarily mediated through a CdMT complex, and that metallothionein is an important intracellular protein for protection against chronic cadmium nephrotoxicity.

When metallothionein-bound cadmium is transported to the kidney, it is readily diffusible and filterable at the glomerulus and may be effectively reabsorbed from the glomerular filtrate by the proximal tubule cells (Foulkes 1978). Exogenous metallothionein is degraded in lysosomes; this process may release cadmium, which may induce fresh metallothionein synthesis in the proximal tubule (Squibb et al. 1984). Cadmium induced renal toxicity is probably associated with cadmium not bound to metallothionein (Goyer et al. 1989; Norniyama and Nomiyama 1986); however, brush-border membranes of the renal tubule may be damaged by cadmium that is bound to metallothionein (Suzuki and Cherian 1987). Renal damage is believed to occur if the localization of cadmium or an excessive concentration of cadmium prevents it from becoming bound to metallothionein.

The route of cadmium administration does not appear to affect the metallothionein metabolism in liver and kidney, although inhalation exposure induces metallothionein in the lung (Glaser et al. 1986; Hart 1986) and oral exposure induces metallothionein in the intestine (Muller et al. 1986). Parenteral administration of cadmium can result in doses high enough to overwhelm the endogenous metallothionein content and thereby cause effects on tissues that appear to be to protected by metallothionein synthesis after inhalation or oral exposure (Sendelbach and Klaassen 1988).

2.3.4 Elimination and Excretion

Most cadmium that is ingested or inhaled and transported to the gut via mucociliary clearance is excreted in the feces. However, almost all excreted cadmium represents material that was not absorbed from the gastrointestinal tract. Most absorbed cadmium is excreted very slowly, with urinary and fecal excretion being approximately equal (Kjellstrom and Nordberg 1978). Half-times for cadmium in the whole body of mice, rats, rabbits, and monkeys have been calculated to be from several months up to several years (Kjellstrom and Nordberg 1985). Half-times in the slowest phase were from 20 to 50% of the maximum life span of the animal (Kjellstrom and Nordberg 1985). In the human body, the main portion of the cadmium body burden is found in the liver and kidney and in other tissues (particularly muscle, skin, and bone). After reviewing the literature, Kjellstrom and Nordberg (1985) developed a range of half-times from their kinetic model for the human kidney of between 6 and 38 years, and for the human liver of between 4 and 19 years.

2.3.4.1 Inhalation Exposure

Cadmium excretion in urine of occupationally exposed workers increases proportionally with body burden of cadmium, but the amount of cadmium excreted represents only a small fraction of the total body burden unless renal damage is present; in this case, urinary cadmium excretion markedly increases (Roels et al. 1981b). Fecal excretion in workers occupationally exposed to cadmium reflects mainly cadmium dust swallowed from industrial air and/or incidentally ingested from contaminated hands (Adamsson et al. 1979).

In rats, following a 2-hour inhalation exposure to cadmium carbonate, cadmium was primarily eliminated in the feces, with a minor component (approximately 1% of fecal excretion) in the urine (Rusch et al. 1986). Cadmium excretion by both routes declined with time after exposure, with significantly elevated excretion found at 7 days, but not 30 days, after exposure (Rusch et al. 1986). Most of the cadmium initially excreted in the feces was probably not absorbed, but rather represented particles transported from the lung to the gastrointestinal tract (Moore et al. 1973).

2.3.4.2 Oral Exposure

Following oral exposure, the major proportion of administered cadmium is found in the feces, because absorption is so low (see Section 2.3.1.2) (Kjellstrom et al. 1978). Among 5 healthy adult volunteers, fecal excretion of a single dose of radiolabeled cadmium declined with time up to 45 days after ingestion, while urinary excretion remained at a low, near-constant level (Rahola et al. 1973). After about 20 days, fecal and urinary excretion appeared to be comparable (Rahola et al. 1973). In contrast, among 4 healthy adults ingesting cadmium in intrinsically labeled crabmeat, fecal excretion was 30 times higher than urinary excretion up to 10 weeks after ingestion of the test meal (Newton et al. 1984). In rats orally exposed to up to 0.35 mg/kg/day of cadmium in the diet for 60 days, no significant increase in urinary cadmium content was found (Weigel et al. 1984). The overall excretion of absorbed cadmium is slow, with biological halftimes of 70-270 days in rats or mice orally exposed to cadmium (Engstrom and Nordberg 1979; Moore et al. 1973).

In a comprehensive model developed for human cadmium toxicokinetics, parameters for urinary and fecal excretion were derived by adjustments to empirical data derived from human and animal studies

(Kjellstrom and Nordberg 1978, 1985). Fecal excretion constitutes unabsorbed cadmium plus "true" excretion originating from blood via the intestinal wall (a function of cadmium body burden) and from bile via the liver (a function of cadmium liver burden) (Kjellstrom and Nordberg 1985). Urinary excretion depends on blood concentration and kidney concentration, and total excretion is assumed to equal daily intake at steady state. Using these methods and assumptions, daily fecal and urinary excretion are estimated to be 0.007 and 0.009% of body burden, respectively (Kjellstrom and Nordberg 1978, 1985).

Groups of 10 female outbred albino rats were exposed to cadmium in drinking water (as $CdCl_2$) at 0 or 4.8 mg/kg/day for 10 weeks (at 4 weeks prior to mating, at 3 weeks of gestation, or 3 weeks into lactation). After weaning, exposure to cadmium was terminated. In dams, kidney concentrations exceeded liver concentrations, while in pups, the renal and liver concentrations were similar at all times during exposure. In pups, both hepatic and renal cadmium concentrations considerably increased only during the second half of the lactation period (Ld 11-21). The concentrations in the dams were several orders higher than in the offspring. After discontinuation of exposure, organ concentration slightly decreased in dams (2% in liver and 12% in kidneys), while in pups the decrease was 84% in the liver and 62% in the kidneys. These values do not indicate cadmium elimination but rather dilution caused by growth (Kostial et al. 1993).

2.3.4.3 Dermal Exposure

No studies were located regarding excretion in humans after dermal exposure to cadmium. Cadmium was reportedly detected in urine in guinea pigs dermally exposed to aqueous cadmium chloride, but no details are available (Skog and Wahlberg 1964).

2.3.5 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) are 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 2-3 shows a conceptualized representation of a PBPK model.

If PBPK models for cadmium exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

2.3.5.1 Summary of Cadmium PBPK Models

Several models have been reported to describe the kinetics of cadmium in mammalian systems. Of these models, the Nordberg-Kjellstrom model (Kjellstrom and Nordberg 1978; Nordberg and Kjellstrom 1979) has been the most widely used for cadmium risk assessment. Three of the most relevant cadmium models will be discussed here.

2.3.5.2 Cadmium PBPK Model Comparison

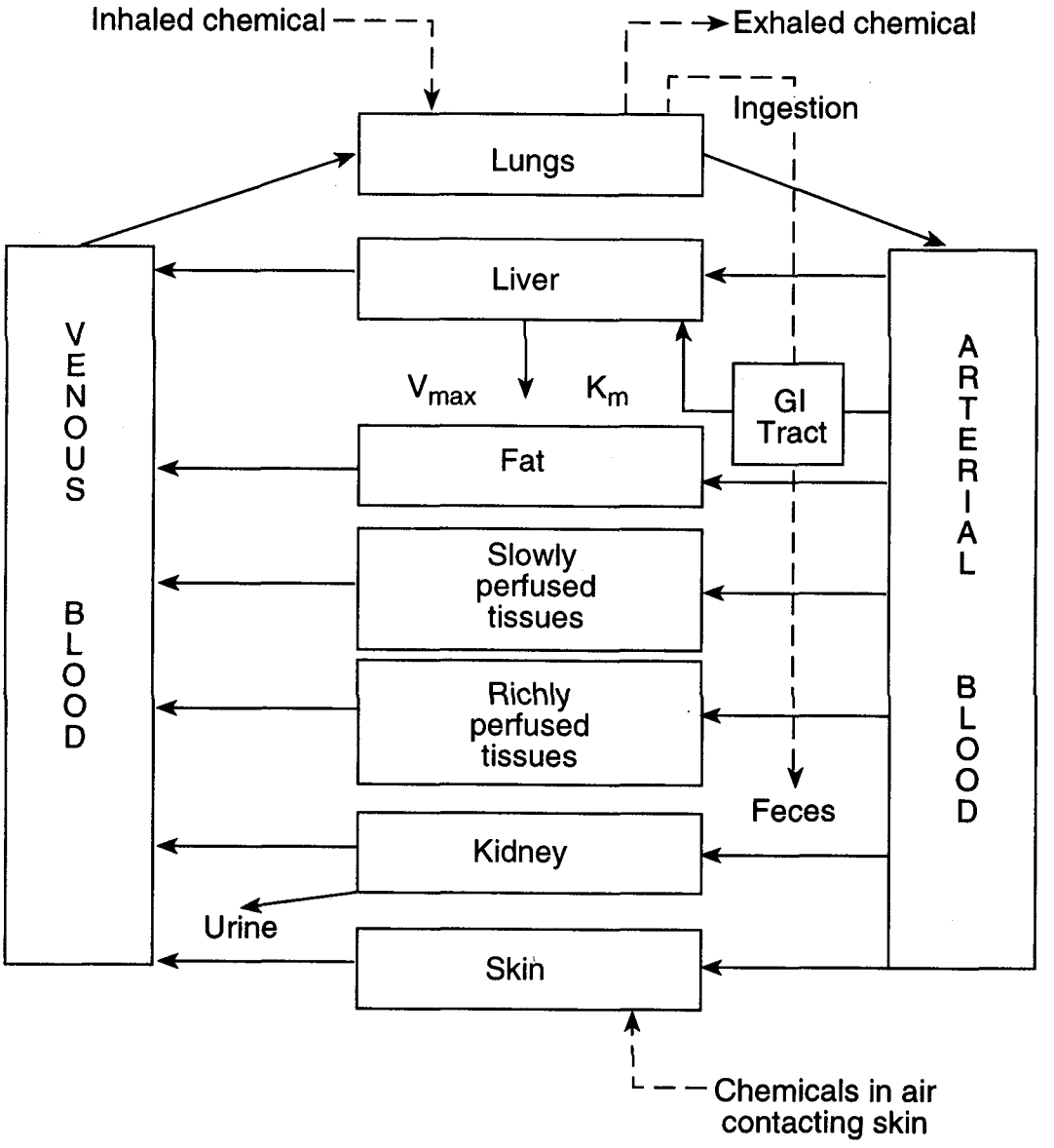
Although the Nordberg-Kjellstrom model (Kjellstrom and Nordberg 1978; Nordberg and Kjellstrom 1979) has its limitations, it provides the best overall description of cadmium toxicokinetics and is largely based on human data. The Shank (Shank et al. 1977) and Matsubara-Khan (Matsubara-Khan 1974) models are not as useful for human risk assessment applications, but they do provide useful insights into the absorption, distribution, and compartmentalization of cadmium in laboratory animals. These insights may have some future use in human risk assessment as PBPK models for cadmium continue to be refined.

2.3.5.3 Discussion of Cadmium Models

The Nordberg-Kjellstrom Model

The Nordberg-Kjellstrom model (Kjellstrom and Nordberg 1978; Nordberg and Kjellstrom 1979) is a linear multicompartment model that is the most commonly used model for cadmium risk assessment work today. The Nordberg-Kjellstrom schematic model diagram is shown in Figure 2-4.

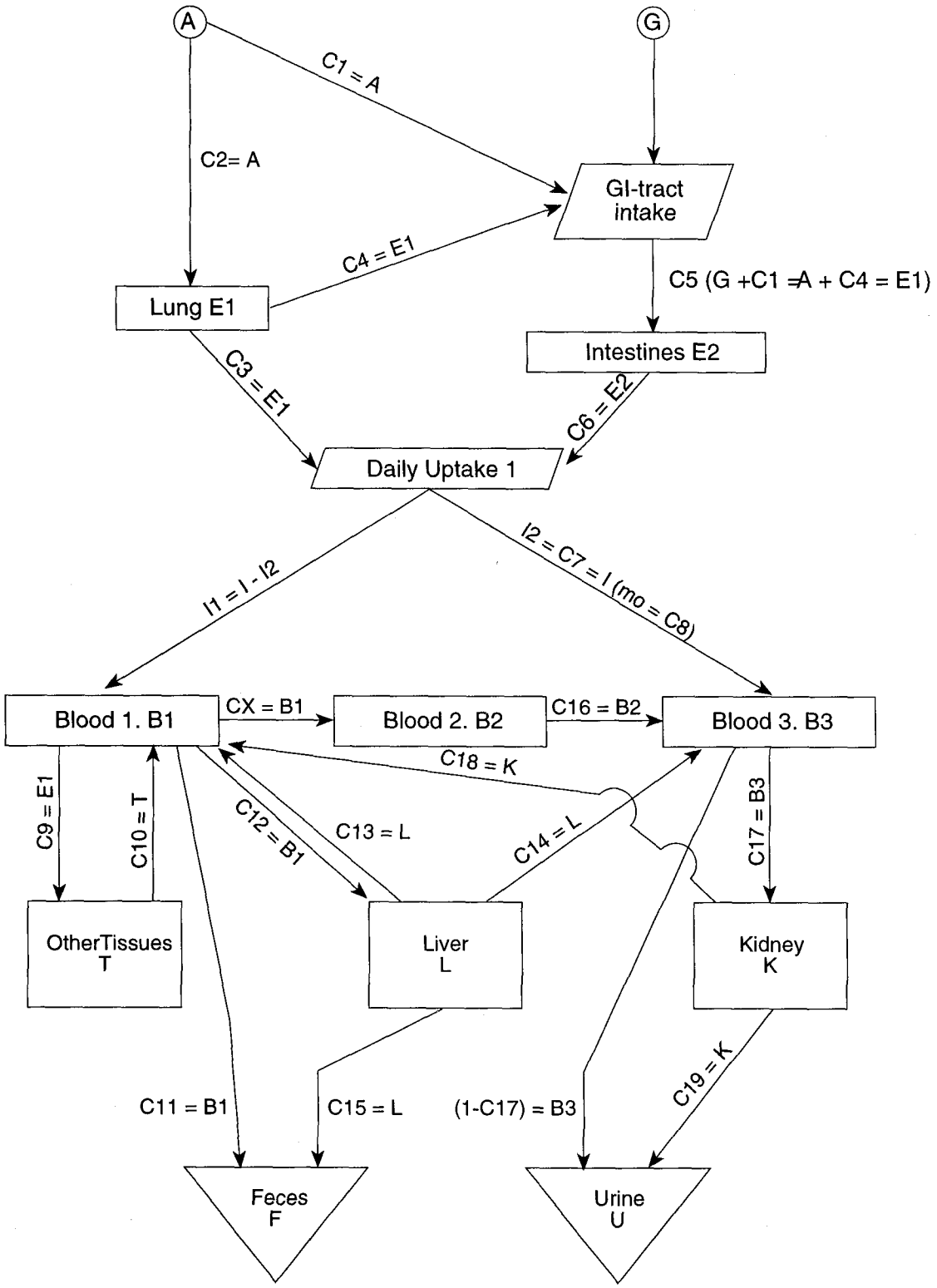
Figure 2-3. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



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.

Figure 2-4. A Schematic Representation of the Nordberg-Kjellström Model



Risk assessment. The Nordberg-Kjellstrom model has been demonstrated to be a useful model in human risk assessment work. Frazier (1994), however, noted that the model has two major limitations: (1) the linear nature of the model may not adequately allow a good description of known nonlinearities in biological responses to cadmium dosing, and (2) the phenomenological approach taken with this model does not provide a foundation for incorporating biological variability into the model parameters.

Description of the Model. The Nordberg-Kjellstrom model (see Figure 2-4) is a linear multicompartment model that describes the disposition of cadmium via the oral and inhalation routes of exposure only. Dermal exposure and subsequent absorption through the skin were assumed to be negligible in this model. For inhalation exposures, the model accounts for different deposition patterns for different size particles in nasopharyngeal, tracheobronchial, and alveolar regions of the respiratory tract. Particles with mass median aerodynamic diameter (MMAD) of 5 pm (i.e., cadmium-laden dust) were assumed to distribute mainly to the nasopharyngeal region (75%) with lesser amounts depositing in the alveolar (20%) and tracheobronchial (5%) regions. Particles of 0.05 pm MMAD (i.e., cigarette smoke) were assumed to deposit 55% in the alveolar compartment, 10% in the tracheobronchial compartment, and none in the nasopharyngeal compartment. The remaining amounts are exhaled For all particle sizes initially deposited in the nasopharyngeal and tracheobronchial compartments, mucociliary clearance clears some particles from the respiratory tract to enter the oral compartment for absorption or out of the body and back to the environment. Assumed model coefficient values and the available physiological parameters are shown in Table 2-4.

For the oral route of exposure, cadmium may enter the gastrointestinal tract via food or water contaminated with cadmium, or as cadmium particles embedded in mucus from the respiratory tract via the mucociliary/tracheobronchial escalator. By either route of exposure, the model assumes that cadmium enters into any of three blood compartments (B) (see Figure 2-4). Bl is the plasma compartment where cadmium may bind to plasma components (i.e., albumin and other organic constituents). B2 is the redblood cell compartment which represents the accumulation of cadmium in erythrocytes, while B3 represents the binding of cadmium to metallothionein. The model does not take into account induction of metallothionein after cadmium exposure. From the blood, cadmium is calculated to distribute to either the liver, kidney, or “other tissues,” the major accumulation sites. Elimination is either via the feces or in the urine. The transport of cadmium between the compartments is assumed to follow first-order exponential functions and is driven on concentration-dependent gradients.

Table 2-4. Assumed Model Parameters and Some Physiologic Parameters for the Nordberg-Kjellström Model

Coefficient or parameter	Assumed range	Unit[a]	Values fitting to empirical data
	Model parameters		
C1	0.1–0.2 (cigarette smoke)		0.1
	0.4–0.9 (factory smoke)		0.7
C2	0.4–0.6 (cigarette smoke)		0.4
	0.1–0.3 (factory smoke)		0.13
C3	0.01–0.3	day^{-1}	0.05
C4	*0.1 x C3 = 0.001–0.03*	day^{-1}	*0.005*
C5	0.03–0.1		0.048
C6	0.05	day^{-1}	0.05
C7	0.2–0.4		0.25
C8	0.5–5.0	µg	1
C9	0.4–0.8		0.44
C10	0.00004–0.0002	day^{-1}	0.00014
C11	0.05–0.5		0.27
C12	0.1–0.4		0.25
C13	0–0.0001	day^{-1}	0.00003
C14	0.0001–0.0003	day^{-1}	0.00016
C15	0–0.0001	day^{-1}	0.00005
C16	*0.004–0.015*	day^{-1}	*0.012*
C17	0.8–0.98		0.95
C18	0–0.0001	day^{-1}	0.00001
C19	0.00005–0.0002	day^{-1}	0.00014
CX	0 01–0.05		0.04
C20	0.05–0.5		0.1
C21	0–0.000002	day^{-1}	0.0000011
	Physiologic parameters		
Average liver weight	1,500	gram	
Average blood volume	70	mL/kg	
Average blood specific gravity	1.06		
Average daily urine excretion (adult)	1.0	L	
Average daily urine excretion (aged)	0.9	L	
Average daily urine excretion (child)	0.5	L	

[a]Blanks indicate a unitless value

Validation of the model. The Nordberg-Kjellstrom model was validated using several independent sets of human data from both Sweden and Japan. The data set by Friberg et al. (1974) estimated that smoking 20 cigarettes a day would result in an inhalation of 2-4 μg/day of cadmium, assuming smoking started at 20 years of age and daily cadmium intake from food was 16 μg/day. Based on the Friberg et al. (1974) data, the model predictions of cadmium concentrations in the kidney agreed well with the observed data from a study by Elinder et al. (1978); however, the model predicted higher than expected values for liver cadmium compared to the observed data from the Elinder study. The model's urinary excretion of cadmium (0.84 μg/24 hours for a 50-year-old person) agreed well with the observed data (0.56-0.8 μg/24 hours). The model predicted blood cadmium levels for Swedish smokers to be about 2 ng/g which compared well to the actual concentration of 1.6 ng/g.

The model was also validated against a data set for an average 45year-old Japanese person living in Tokyo whose daily intake of cadmium is 40 μg via food and 2.7 μg via the inhalation route. Subjects were assumed to be smokers averaging 24 cigarettes a day starting at age 20. Based on these exposure conditions, the measured values for cadmium in the kidney, liver, and "other tissues" (in this case, muscle only) were reported to be 65, 3.4, and 0.2 μg/g, respectively, with the model predicting 48, 3.2, and 0.18 μg/g. For blood and urine, the measured values were 4.5 μg/g for blood and 1.1 μg/L for urine; the model predicted 3.4 μg/g and 1.3 μg/24 hours (assuming 1 L of urine output/day, the value would be 1.3 μg/L).

Another study of Japanese people reported cadmium concentrations in urine in relation to high cadmium concentrations in rice in their daily diet. For people who consumed rice containing 0.04 μg/g of rice (240 μg/day), the observed urinary level of cadmium was 7 μg/L; consumption of rice containing 1.1 μg cadmium/g of rice (660 μg/day), resulted in an observed value of 14 μg/L of urine. After making certain assumptions about the average daily consumption of rice containing an assumed amount of cadmium, and assuming an average urine production of 1 L/day, the model calculated urinary levels of 4.8 and 15.5 μg/L of urine, agreeing well with the observed values.

The model was also validated against a data set with high concentrations of cadmium in air (50 $\mu g/m^3$) (Piscator 1972) and blood cadmium concentrations ranging from 10 to 50 ng/g whole blood. Calculated blood, urine, liver, and kidney levels of cadmium agreed only roughly with the observed values; however, the authors concluded that the model predictions may not be accurate based on the observations that workers with long exposure histories had most likely experienced higher exposure levels in the past,

skewing the data set, resulting in poor model predictions. Another data set by Piscator (1974) involved a group of Swedish workers involved in polishing cadmium-plated objects, who were exposed to high concentrations of cadmium for 2 years or less. Cadmium levels were measured in the urine and blood. When this exposure data set was input into the model, the model could not adequately predict blood and urine levels for these workers.

Target tissues. The Nordberg-Kjellstrom model assumes that the kidney and liver are the two specific target tissues in which cadmium accumulates. The model also accounts for all other tissue accumulation in the "other tissues" compartment (i.e., muscle). The model assumes a human liver tissue half-life ($t_{1/2}$) of 4-19 years and a kidney $t_{1/2}$ of 6-38 years. For the "other tissue" compartments, $t_{1/2}$ was assumed to be 9-47 years. The Nordberg-Kjellstrbm model does account for the loss of renal tubular epithelial cells leading to a loss of tubular reabsorptive capacity. This loss of cells could conceivably result in an increase in the excretion of cadmium from the tubules and an increase in the transport of cadmium from the tubules to the blood. This loss of cells is theorized to account for the large $t_{1/2}$ range for cadmium in the kidney. The model assumed that no changes in the movement of cadmium from the kidney to blood occurred with age and that the loss of cadmium from the kidney to the urine increased linearly after the age of 30.

The Nordberg-Kjellstrom model also accounted for differences in kidney and liver weights among different age groups and between peoples of different ethnic origins. The model corrected for differences in liver, kidney, blood, and "other tissue" weights with relation to age (1 and 79 years of age) and ethnicity (Japan and Sweden).

Species extrapolation. The Nordberg-Kjellstrom model was based solely on data collected from humans and was intended for human risk assessment applications. The model did not address any potential application for this model of cadmium in laboratory animals.

High-low dose extrapolation. The Nordberg-Kjellstriim model has been shown to adequately predict fluid and tissue concentrations via the oral and inhalation routes of exposure for humans exposed to low doses of cadmium. However, the model has difficulty in adequately predicting fluid and tissue concentrations in humans exposed to high concentrations of cadmium, especially for those individuals exposed to high concentrations via the inhalation route.

Interroute extrapolation. The Nordberg-Kjellstrom model adequately predicted the fate of cadmium in target tissues after exposure via the inhalation and oral routes. The dermal route of exposure was not incorporated into the model parameters and was considered an insignificant route of exposure in humans.

The Shank Model

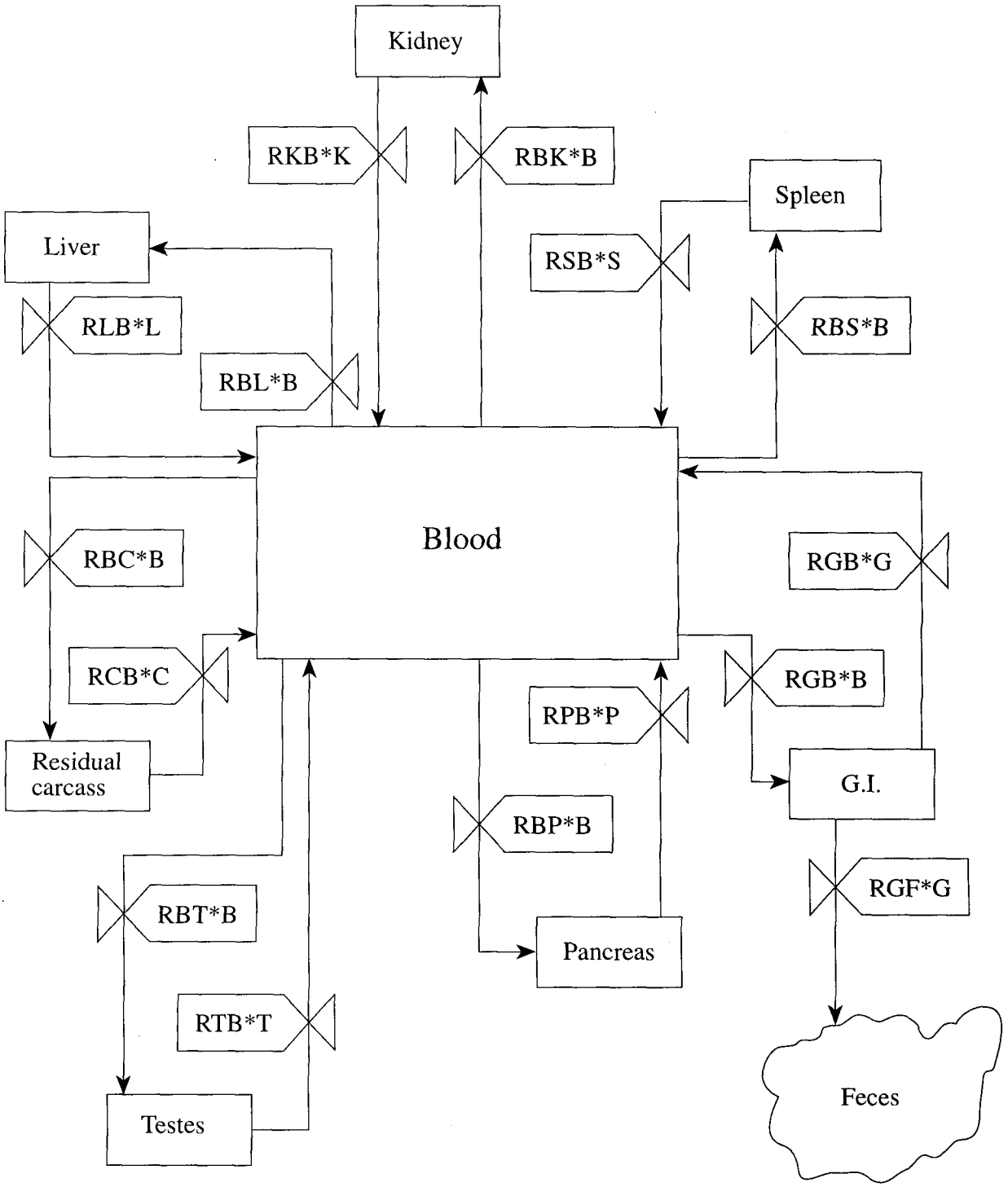
Risk assessment. The Shank model (Shank et al. 1977) may have the potential to serve as an alternative mathematical model for predicting the retention of cadmium in biological systems. Unfortunately, no human data were used to validate the Shank model for use as a risk assessment tool in cases of human exposure. In addition, the Shank model was validated only for the intravenous and subcutaneous routes of exposure; no data were presented for the oral, inhalation, or dermal routes of exposure.

Description of the model. A schematic representation of the Shank model is illustrated in Figure 2-5. The model mathematically represents the dynamic transport of cadmium between compartments in a mammalian biological system based on the male adult SW/NIH mouse as the test animal species. The intent was to predict the retention of cadmium in other species of animals (including humans) without requiring an adjustment of species-specific rate constants from within the model.

Male adult mice of the SW/NIH strain were dosed intravenously with ^{109}Cd as ^{109}Cd acetate. Mice received from 1 to 3 intravenous injections spaced 48 hours apart. Animals in each group were sacrificed at 2 minutes, 10 minutes, 1 hour, 10 hours, and 48 hours after the last dose. Tissues (liver, kidney, pancreas, spleen, gastrointestinal tract, testes, carcass, and feces) were harvested and the radioactivity recorded. A 9-compartment model was derived. Cadmium kinetics between compartments are described by first-order kinetics. The individual compartment retention values, obtained from the distribution study, were incorporated into the model equations and the rate constants derived.

Validation of the model. The Shank model was validated using three independent data sets. Mann (1973) dosed dogs, goats, and sheep with one intravenous injection of ^{109}Cd acetate (30 μCi), and the liver and kidneys were examined for cadmium content 8 weeks after administration. The Shank model's predicted values of cadmium retention in liver and kidneys at 8 weeks after a single administration were in good agreement with the observed values of the Mann (1973) study in all three species. Only data from the

Figure 2-5. A Schematic Representation of the Shank Model



Source: adapted from Forrester 1968

liver and kidneys were available for evaluation. A data set from a study by Gunn et al. (1968) was used to evaluate the ability of the Shank model to predict the retention of cadmium in liver and kidney after a single subcutaneous administration of $CdCl_2$ Animals in that study were sacrificed 2 weeks after administration, and the liver and kidneys were examined for cadmium content. The model values for the same time period were in very close agreement with observed values. Again, only data from the liver and kidneys were available for evaluation. Finally, a data set by Shanbaky (1973) was used to test the model's validity with multiple injections of cadmium acetate in rats. Five injections of cadmium acetate were administered over a 48-hour period; liver, kidneys, pancreas, spleen, and gastrointestinal tract were examined for cadmium content. The Shank model was found to be in close agreement with the arithmetic means of observed values found in the Shanbaky (1973) study.

No human data were presented to validate the model's effectiveness in predicting the cadmium retention in human target tissues after either a single or multiple dosing regime.

Target tissues. The target tissues for this model included the liver, kidney, pancreas, spleen, gastrointestinal tract, testes, and carcass of laboratory animals. No human tissue was used to derive cadmium retention in any of these tissues.

Species extrapolation. The model used goats, dogs, rats, mice, and sheep with various doses and dosing schemes of cadmium acetate and cadmium chloride and was found to serve as a good predictor of cadmium retention in the target tissues listed above. No human data were presented to determine if the model could satisfactorily predict the cadmium retention in human target tissues.

High-low dose extrapolation. High- and low-dose extrapolation was not specifically addressed by the Shank model.

Interroute extrapolation. Interroute extrapolations were addressed in a limited fashion by the Shank model. The model appeared to adequately predict the amount of cadmium retention in the target organs of laboratory animals, in particular the liver and kidney, when dosed by either the intravenous or subcutaneous routes. The inhalation and dermal routes of exposure, and other parenteral routes of exposure (intramuscular, intraperitoneal, intradermal, etc.) were not addressed by the Shank model. No human data were presented to determine if interroute extrapolations were valid.

The Matsubara-Khan Model

Risk assessment. The Matsubara-Khan model (Matsubara-Khan 1974) has not been used as a tool in risk assessment for humans. This model does demonstrate that cadmium kinetics and biological half-lives vary by tissue.

Description of the model. The Matsubara-Khan model is a simple model that attempted to fit cadmium elimination kinetic parameters into either a l- or 2-compartment model. To obtain the data for the model, male and female ICR mice (8 weeks of age) were administered a single subcutaneous injection of a known amount of $^{109}CdCl_2$. Specific groups of mice were sacrificed at 1, 2,4, 8, 16, 32, 64, or 128 days after injection. At the time of sacrifice, blood, liver, kidney, salivary gland, stomach wall and stomach contents, small intestine and small intestine contents, and colon wall and colon contents were removed and the amount of ^{109}Cd remaining in these tissues was determined.

An oral study was conducted in conjunction with the subcutaneous study described above. In the oral study, 8-week-old male mice (ddd x BALB/c; Fl) were orally administered $^{115m}CdCl_2$ by gavage. Groups of mice were sacrificed at 1, 2, 4, 8, 16, 32, 64, or 128 days after injection. At the time of sacrifice, liver, kidney, salivary gland, stomach wall, gonad, and spleen were removed and the amount of ^{115m}Cd remaining in these tissues was determined.

The rate of uptake, rate constants, and biological half-lives determined for the subcutaneous and orally dosed mice are summarized in Table 2-5. Matsubara-Khan found that tissue kinetics in mice dosed subcutaneously with $^{109}CdC1_2$, fit into either a l- or 2-compartment model, depending on the tissue. The data from the digestive tract organs (stomach wall, small intestine, and colon) were best fitted into *a* l-compartment model, with a strained fit of the data from the digestive tract contents (stomach, small intestine, and colon contents) to the 1-compartment model. Data from the blood, liver, kidneys, and salivary glands were best fitted to the 2-compartment model. Extremely small second-rate constants in the kidneys and salivary glands indicate that the elimination of cadmium from these tissues is very slow. For the oral study, similar findings were observed, with data from the gonads and spleen fitting the l-compartment model best. Biological half-lives were invariably longer for the subcutaneously dosed animals, while the rate constants were slightly smaller for the subcutaneously dosed animals. Sex-related

Table 2-5. Estimated Parameters, Rate of Uptake, Rate Constants and Biological Half-Lives in Selected Mouse Organs after Subcutaneous and Oral Administrations of $^{109}CdCl_2$

Organ	Rate of uptake (95% CL)		Rate constants b and c (95% CL)		Biological half-life (days)	
	SC	PO	SC	PO	SC	PO
Liver	21	8.7	0.011 0.57	0.016 0.91	631.2	430.76
Kidney	22	1.4	0.0007 0.30	0.0016 0.30	9902.3	4332.3
Salivary gland	21	0.33	0.0016 0.73	0.0047 0.78	4330.95	1500.89
Blood	0.15	NM	0.024 0.65	NM	291.1	
Stomach wall	1.7	0.36	0.0073	0.017	95	41
Stomach contents	0.68	NM	0.062	NM	11	NM
Small intestine	0.95	NM	0.01	NM	69	NM
Small intestine contents	2.5	NM	0.067	NM	10	NM
Colon	1.4	NM	0.013	NM	53	NM
Colon contents	4.1	NM	0.15	NM	4.6	NM
Gonad	NM	0.37	NM	0.012	NM	58
Spleen	NM	0.44	NM	0.0011	NM	630

CL = confidence limits; PO = oral; SC = subcutaneous; NM = Not measured

Source: adapted from Matsubara-Khan 1974

differences in rate of uptake, rate constants, and biological half-lives were not found, except in the kidney data in which females had slightly smaller rate constants.

Validation of the model. No independent data sets were used to validate the Matsubara-Khan model.

Target tissues. For the subcutaneous injection study, the Matsubara-Khan model used blood, liver, kidney, salivary gland, stomach wall and stomach contents, small intestine and small intestine contents, and colon wall and colon contents. For the oral study, the model used liver, kidney, salivary glands, stomach wall, gonads, and spleen.

Species extrapolation. No species extrapolations were performed in the Matsubara-Khan model.

High-low dose extrapolation. No high-low dose extrapolations were performed in the Matsubara-Khan model.

Interroute extrapolation. The Matsubara-Khan model compared the oral and subcutaneous routes and reported similar rate constants for many of the tissues examined. Biological half-lives varied considerably for the kidney and salivary gland, but were not much different for liver between the two routes of exposure.

2.4 MECHANISMS OF ACTION

2.4.1 Pharmacokinetic Mechanisms

Absorption. Cadmium can be absorbed by the inhalation, oral, and dermal routes of exposure regardless of its chemical form (chloride, carbonate, oxide, sulfide, sulfate, or other forms). Absorption by the dermal route of exposure, however, is relatively insignificant for cadmium, although small amounts are absorbed percutaneously over a long period of time (Wester et al. 1992). Absorption is mainly ofconcern from inhalation and oral exposures.

Gastrointestinal tract absorption of cadmium (in any chemical form) is relatively low when compared to the total amount of cadmium absorbed via the inhalation route. Gastrointestinal tract absorption of cadmium

has been determined to be l-2% in mice and rats (Decker et al. 1958; Ragan 1977), 0.5-3.0% in monkeys (Nordberg et al. 1971), 2% in goats (Miller et al. 1969), 5% in pigs and lambs (Cousins et al. 1973; Doyle et al. 1974), and nearly 16% in cattle (Miller et al. 1967). Lehman and Klaassen (1986) investigated whether the disposition of cadmium in male Sprague-Dawley rats is dependent on dose. The concentration of cadmium in tissues increased more than the increase in an oral dosage, and low dosages of cadmium (1 and 10 μg/kg) distributed preferentially to the kidney, suggesting that cadmium may be absorbed as a Cd-metallothionein complex at low dosages. The percentage of the po dosage retained 7 days after administration increased from 0.40% at the 1 μg/kg dosage to 1.65% at the 100 μg/kg and higher dosages. At a 1 μg Cd/kg po dosage, approximately 60% of cadmium in intestinal cytosol was bound to metallothionein, whereas at the 10,000 μg Cd/kg dosage, approximately 50% of the cadmium was bound to metallothionein. The results indicate that the retention of cadmium after ingestion is dosage-dependent and results from increased absorption of cadmium at higher dosages. Goon and Klaassen (1989) measured absorption of cadmium in rat intestine in situ and reported that the intestinal absorption of cadmium is dosage independent at low dosages of cadmium (<10 μg/kg) and dosage dependent at high dosages (>10μg/kg). They also evaluated the role of metallothionein and concluded that saturation of intestinal metallothionein is not a major determinant of the observed dosage-dependent absorption of cadmium.

In humans, cadmium absorption has been reported to be as much as 3-8%. Several blood and dietary factors can influence the absorption of cadmium from the gastrointestinal tract. Dietary deficiencies of calcium or iron and diets low in protein content can enhance cadmium absorption. Low blood ferritin content in women has been demonstrated to double the absorption of cadmium from the gastrointestinal tract. Zinc decreases the dietary absorption of cadmium.

In some cases, cadmium bound to metallothionein (as in food) is not absorbed or distributed from the gastrointestinal tract as readily as ionic cadmium. Mice had lower blood and liver cadmium levels from oral exposure to CdMT, compared to levels from cadmium chloride exposure for comparable doses, but the CdMT resulted in higher kidney cadmium levels. Maitani et al. (1984), however, report that less cadmium was absorbed when rats received Cd-TH in saline than $CdCl_2$ in saline. Cd-TH added to liver homogenate or liver homogenate containing Cd-TH increased the absorption of cadmium, resulting in renal cadmium levels similar to those in mice receiving $CdCl_2$ in saline. Sharma et al. (1983) reported that human exposure to very high intakes of cadmium during the consumption of oysters did not greatly elevate the whole blood and urine cadmium levels proportional to the level of intake

A higher fraction of inhaled cadmium than ingested cadmium is absorbed. The total amount of cadmium absorbed by the body via the lungs depends on the particle size. Larger particles are deposited in the nasopharyngeal and tracheobronchial airways via impaction, and are largely cleared by mucociliary processes, leading to absorption by the gastrointestinal tract. Smaller particles reach the smaller airways and alveoli, and depending on the particle's solubility, are absorbed and distributed to the rest of the body. Solubility in lung fluids plays a role in absorption from the lung into the body of cadmium salts. Theoretically, the highly soluble salts, chloride, nitrate, acetate, and sulfate would be expected to give the highest blood levels following inhalation exposure to a given air concentration. The insoluble cadmium salts, the various sulfides, should yield the lowest blood level. The lung, however, is rich in carbon dioxide that is continuously transferred from the blood. Particles of the various cadmium sulfides within the lung can react with this carbon dioxide. Lung tissue may then absorb and transfer solubilized or released cadmium ions to the blood.

No direct data, however, are available on cadmium deposition, retention, or absorption in the human lung. Data from animal studies indicate that lung retention is greatest after short-term exposure, 5-20% after 15 minutes to 2 hours (Barrett et al. 1947; Henderson et al. 1979; Moore et al. 1973; Rusch et al. 1986). The initial lung burden declines slowly after exposure ceases (Henderson et al. 1979; Moore et al. 1973; Rusch et al. 1986), due to the absorption of cadmium and the lung clearance of deposited particles. After longer periods of inhalation exposure to cadmium, somewhat lower lung retentions are found (Glaser et al. 1986). The absorption of cadmium in the lung differs somewhat among chemical forms, but the pattern apparently does not correlate well with solubility in water (Glaser et al. 1986; Rusch et al. 1986). Retention of cadmium has been reported to be >40% in rats (Moore et al. 1973) 40% in canines (Friberg et al. 1974), and 10-20% in mice (Potts et al. 1950).

According to Elinder et al. (1985), one cigarette may contain up to 2 μg of cadmium (10% of which is inhaled). Based on comparison of cadmium body burdens in human smokers and nonsmokers, cadmium absorption from cigarettes appears to be higher than absorptions of cadmium aerosols measured in animals (Nordberg et al. 1985). The chemical form of cadmium in cigarette smoke is likely to be similar to that produced by other combustion processes, primarily cadmium oxide aerosols. The greater absorption of cadmium from cigarette smoke is likely due to the very small size of particles in cigarette smoke and the consequent very high alveolar deposition (Nordberg et al. 1985).

Distribution and Metabolism. Once absorbed, cadmium is distributed to most tissues of the body, but tends to concentrate in the liver and kidneys of all animals, independent of the form. Cadmium enters the blood and may bind to plasma proteins (albumin, globulins, etc.), plasma metallothionein, or directly to the erythrocyte. Spleen, pancreas, and testes also have relatively high concentrations of cadmium after oral or inhalation exposures. Cadmium is not known to undergo any direct metabolic conversion such as oxidation, reduction, or alkylation. The cadmium (+2) ion binds to anionic groups in proteins and other molecules. The sulfhydryl groups in albumin and metallothionein have a particularly high affinity for cadmium (Nordberg et al. 1985).

Shaikh et al. (1993) report that disposition of cadmium in mouse liver, kidney, and testes is different for different strains, sex, or age. Different dose levels (i.e., subcutaneous doses in the 5-30 umol/kg body weight range) also altered the disposition. Liver cadmium levels and metallothionein levels did not always correlate with hepatotoxicity. The difference in the tissue accumulation of cadmium may relate to variations in the hormonal or other intrinsic factors that affect cellular uptake of cadmium, subcellular distribution of cadmium, or metallothionein metabolism.

In 10-day-old rats, high levels of metallothionein (young rats innately have high levels of metallothionein compared to adults) have been reported to play an important role in their resistance to liver damage, presumably by binding and retaining cadmium (Goering and Klaassen 1984). There was a 67% increase in liver cadmium levels in the young compared to the adult, but this is not as dramatic as the 10-fold increase in liver metallothionein. Wong and Klaassen (1980a) reported only a 30% increase in liver cadmium in 4-day-old rats compared to the adults, but a 10-fold difference in liver metallothionein compared to the adults. These and other tissue distribution data led Wong and Klaassen to propose that metallothionein does not play a major role in the tissue distribution and retention of cadmium in the young.

More recent studies support this hypothesis. Liu and Klaassen (1996) evaluated the use metallothionein-I transgenic (MT-TG) mice to determine whether increased concentrations of metallothionein affected cadmium absorption and distribution. A single dose of ^{109}Cd was given to control and MT-TG mice orally (0.3-300 μmol/kg [200 μCi/kg]) or intravenously (0.03-10 μmol/kg [20 μCi/kg]). Cadmium concentrations in 15 tissues were quantified 7 days later. Higher metallothionein concentrations in tissues of MT-TG mice had no appreciable effects on the concentration of cadmium in tissues compared to controls. An exception to this was the MT-TG mice given the highest dose of cadmium (300 μmol Cd/kg, PO), which had twice the tissue cadmium concentration of controls. Approximately 60% of the cadmium

administered intravenously was retained in the tissues and retention of cadmium in MT-TG mice was similar to that in controls. In both control and MT-TG mice only 0.l-0.3% of cadmium administered po was retained, except for l-3% at the higher doses (100 and 300 μmol/kg). The higher concentrations of metallothionein in MT-TG mice did not appear to inhibit the gastrointestinal absorption of cadmium nor alter the organ distribution of cadmium.

In a companion study on MT-null mice, Liu et al. (1996) report that metallothionein does not play a role in the initial distribution of cadmium to tissues, but does play a major role in the elimination of cadmium, especially from liver, kidney, and pancreas. They conclude that the persistence of cadmium in the body is at least partially due to cadmium binding to metallothionein in tissues. The study investigated the role of metallothionein in the tissue distribution and retention of cadmium using MT-I and -11 null (MT-null) mice. Mice were given $^{109}CdCl_2$ (15 μmol/kg [25 μCi/kg] intraperitoneally), and radioactivity was quantified in 14 major organs at 2 hours, and 1, 2, 3, 7, and 15 days thereafter. The lack of metallothionein in MT-null mice 2 hours after cadmium administration (74% versus 72% of the dose, respectively) did not affect distribution. However, the elimination of cadmium was much faster in MT-null mice than in control mice. In control mice, approximately 40% of cadmium administered was found in the liver 24 hours after administration, and the majority was bound to metallothionein. In contrast, only 20% of cadmium was found in the liver of MT-null mice, which was not bound to metallothionein. Cadmium concentrations in kidney, pancreas, and spleen were also lower in MT- null than in control mice 1 week after administration. No apparent difference in cadmium retention in other organs was noted between control and MT-null mice over the 15-day period. Cadmium concentration in kidney continued to increase with time in control but not in MT-null mice, indicating that an important source of cadmium in the kidney is the uptake of CdMT.

Excretion. Since little of the cadmium presented to the gastrointestinal tract is absorbed, most of the oral dose is excreted via the feces. After inhalation exposure to cadmium, the initial lung burden of cadmium-laden particles depositing in the nasopharyngeal or central airways will be cleared via the mucociliary mechanisms, possibly undergoing a small amount of absorption by the oral route. The remaining cadmium particles will be absorbed in the lung. Once absorbed cadmium has distributed throughout the body (primarily to the liver and kidney), the amounts of fecal and urinary excretion of cadmium are approximately equal. The amount of cadmium in the urine of occupationally exposed workers increases proportionally with body burden of cadmium, but the amount of cadmium excreted represents only a small fraction of the total body burden unless renal damage is present; in this case, urinary cadmium excretion increases markedly (Roels et al. 1981b).

Klaassen and Kotsonis (1977) evaluated biliary excretion of an intravenous bolus of cadmium chloride in the rat, rabbit, and dog. Marked species variation in biliary excretion was observed with rabbits at about 1/6th the rate of the rats, and dogs about 1/300th the rate of the rats. The bile/plasma concentration ratio of cadmium was highly dose dependent, increasing with higher dose. The bile/liver concentration ratio of cadmium was equal to or much lower than 1 decreasing to <1% for the low dose regimen. Biliary excretion increased approximately 4-fold in rats as the temperatures increased from 30 to 40 ^{o}C. Following the administration of different microsomal enzyme inducers (phenobarbital, spironolactone, pregnenolone-16-α-carbonitrile, or 3-methylcholanthrene), only phenobarbital significantly increased biliary excretion.

2.4.2 Mechanisms of Toxicity

Cadmium is toxic to a wide range of organs and tissues; however, the primary target organs of cadmium toxicity are the kidneys and liver. Organs such as the testis, pancreas, thyroid, adrenal glands, bone, central nervous system, and lung have also been studied for toxic effects.

Changes in the kidney due to cadmium toxicosis have been well established. Chronic exposure to cadmium by the oral or inhalation routes has produced proximal tubule cell damage, proteinuria (mainly lowmolecular weight proteins, such as β_2-microglobulin), glycosuria, amino aciduria, polyuria, decreased absorption of phosphate, and enzymuria in humans and in a number of laboratory animal species. The clinical symptoms result from the degeneration and atrophy of the proximal tubules, or (in worse cases) interstitial fibrosis of the kidney (Stowe et al. 1972). Cadmium has been shown to perturb lipid composition and enhance lipid peroxidation (Gill et al. 1989). Depletion of antioxidant enzymes, specifically glutathione peroxidase and superoxide dismutase, has been proposed as the mechanism of cadmium's cardiotoxic effects (Jamall and Smith 1985a), but subsequent studies showed that cardiotoxic mechanisms other than peroxidation are also present (Jamall et al. 1989). Cadmium has been shown to alter zinc, iron and copper metabolism (Petering et al. 1979) as well as selenium (Jamall and Smith 1985b). Xu et al. (1995) propose that an initiating step in cadmium-induced toxicity to the testes is cadmium interference with zinc-protein complexes that control DNA transcription which subsequently leads to apoptosis. Cadmium sequestration by metallothionein (or a chelator in the case of the Xu et al. [19951 study) prevents cadmium from disrupting zinc-dependent transcriptional controls.

Cardenas et al. (1992) investigated a cadmium-induced depletion of glomerular membrane polyanions and the resulting increased excretion of high-molecular-weight proteins. Interference with glomerular

membrane polyanionic charge may precede the tubular damage as a more sensitive and early response to cadmium (Roels et al. 1993). Acute or chronic doses of cadmium, have also been reported to reduce hepatic glycogen stores and to increase blood glucose levels. Intralobular fibrosis, cirrhosis, focal mononuclear infiltrates, and proliferation of the smooth endoplasmic reticulum are among the non-specific histopathological indicators of cadmium toxicity.

Cadmium complexed with metallothionein from the liver can redistribute to the kidney (Dudley et al. 1985). When metallothionein-bound cadmium is transported to the kidney, it readily diffuses and is filtered at the glomerulus, and may be effectively reabsorbed from the glomerular filtrate by the proximal tubule cells (Foulkes 1978). Exogenous metallothionein is thought to be degraded in lysosomes and released. This non-metallothionein-bound cadmium can then induce new metallothionein synthesis in the proximal tubule (Squibb et al. 1984).

Early work indicated that metallothionein binding decreased the toxicity of cadmium, and the ability of the liver to synthesize metallothionein appeared to be adequate to bind all the accumulated cadmium (Goyer et al. 1989; Kotsonis and Klaassen 1978). The rate of metallothionein synthesis in the kidney is lower than in the liver (Sendelbach and Klaassen 1988), and is thought to be insufficient, at some point, to bind the intrarenal cadmium (Kotsonis and Klaassen 1978). Renal damage is believed to occur when the localization of cadmium, or an excessive concentration of cadmium, is unbound to metallothionein. Acute exposure to low levels of cadmium bound to metallothionein produced an intracellular renal damage as described above (Squibb et al. 1984), but damage to brush-border membranes of the renal tubule has also been reported from metallothionein-bound cadmium (Suzuki and Cherian 1987) suggesting other toxic mechanisms may be present.

More recently, Dorian et al. (1992a) evaluated the intra-renal distribution of ^{109}CdMT injected (intravenously) into male Swiss mice at a nonnephrotoxic dose (0.1 mg Cd/kg) and concluded that CdMT-induced nephrotoxicity might be due, at least in part, to its preferential uptake of CdMT into the S1 and S2 segments of the proximal tubules, the site of Cd-induced nephrotoxicity. In a companion study, Dorian et al. (1992b) reported that this preferential renal uptake was also observed after administration of various doses of [^{35}S]CdM. In contrast to the earlier observed persistency of ^{109}Cd in the kidney after ^{109}CdMT administration, however, ^{35}S disappeared rapidly (with a half-life of approximately 2 hours); 24 hours after injection of [^{35}S]CdMT, there was very little ^{35}S left in the kidneys. These observations

indicate that the protein portion of CdMT is rapidly degraded after renal uptake of CdMT and that the released cadmium is retained in the kidney.

The toxic effects and distribution of cadmium were compared after intravenous injection of ^{109}CdMT at 0.05-l mg Cd/kg body w eight and $^{109}CdC1_2$ at 0.1-3 mg/kg in male Swiss mice (Dorian et al. 1995). CdMT increased urinary excretion of glucose, and protein indicated renal injury, with dosages as low as 0.2 mg Cd/kg. In contrast, renal function was unaltered by $CdCl_2$ administration, even at dosages as high as 3 mg Cd/kg. CdMT distributed almost exclusively to the kidney, whereas $CdCl_2$ preferentially distributed to the liver. However, a high concentration of cadmium was also found in the kidneys after $CdCl_2$ administration (i.e., the renal cadmium concentration after administration of a high but nonnephrotoxic dose of $CdCl_2$ was equal to or higher than that obtained after injection of nephrotoxic doses of CdMT). Light microscopic autoradiography studies indicated that cadmium from CdMT preferentially distributed to the convoluted segments (S1 and S2) of the proximal tubules, whereas cadmium from $CdCl_2$ distributed equally to the various segments (convoluted and straight) of the proximal tubules. However, the concentration of cadmium at the site of nephrotoxicity, the proximal convoluted tubules, was higher after $CdCl_2$ than after CdMT administration. A higher cadmium concentration in both apical and basal parts of the proximal cells was found after $CdCl_2$ than after CdMT administration. The authors suggest that CdMT is nephrotoxic, and $CdCl_2$ is not nephrotoxic because of a higher concentration of cadmium in the target cells after CdMT. Dorian and Klaassen (1995) evaluated the effects of ZnMT on ^{109}CdMT renal uptake and nephrotoxicity and concluded that ZnMT is not only nontoxic to the kidney at a dose as high as 5 μmole MT/kg, but it can also protect against the nephrotoxic effect of CdMT without decreasing renal cadmium concentration.

To further test the hypothesis that nephrotoxicity produced from chronic cadmium exposure results from a Cd-metallothionein complex, Liu et al. (1998) exposed MT-null mice to a wide range of $CdCl_2$ doses, 6 times per week for up to 10 weeks. Renal cadmium burden increased with dose and duration up to 140 μg Cd/g kidney in control mice (i.e., MT normal) with a 150-fold increase in renal metallothionein levels (800 μg MT/g kidney). Renal cadmium was much lower in MT-null mice (10 μg Cd/g), and metallothionein levels were not detectable. The maximum tolerated dose of cadmium (as indicated by routine urinalysis and histopathology measures) was approximately 8 times higher in control mice than in MT-null mice. Lesions were more severe in MT-null mice than in controls, indicating that Cd-induced renal injury is not necessarily mediated through a CdMT complex and that metallothionein is an important intracellular protein for protection against chronic cadmium nephrotoxicity.

The critical concentration of cadmium in the renal cortex that is likely to produce renal dysfunction also remains a topic of intense investigation. Whether the critical concentration of urinary cadmium is closer to 5 μg Cd/g creatinine or to 10 μg Cd/g creatinine, corresponding to about 100 and 200 μg cadmium/g kidney, respectively, is the current focus of the debate. In one analysis, the critical concentration producing dysfunction in 10% of a susceptible population has been estimated to be approximately 200 μg cadmium/g kidney; 50% of the susceptible population would experience dysfunction with a kidney concentration of 300 μg/g (Ellis et al. 1984, 1985; Roels et al. 1983).

2.4.3 Animal-to-Human Extrapolations

The effects of cadmium toxicosis have been studied in humans and in many laboratory animal species. The target organs are similar among species, with the liver and kidneys being the primary organs for cadmium induced toxicosis. Absorption, distribution, and excretion of cadmium after oral and inhalation exposures are roughly similar among species; however, there are some notable differences and caveats. Most estimates of cadmium absorption in animals are somewhat lower than the values found from human studies, particularly after prolonged exposure. Differences in the breathing patterns between rats (obligatory nose breathers) and humans (mouth and nose breathers) may also result in radically different lung burden patterns (and hence, different absorption profiles) of cadmium particles in the lungs. Many of the common laboratory animals (in particular the mouse and rat) provide useful information on the toxic effects of cadmium; due to their relatively short lifespan, however, they may not be as useful from a risk assessment point of view in determining the human lifetime effects from inhaling cadmium in air, or ingesting it in food and water. Rates of synthesis and inducibility of metallothionein also differ among species, sex, and target organ.

Even within species there can be significant differences in metallothionein synthesis, and these differences correlate to the degree of cadmium toxicity observed (e.g., the mouse) (Shaikh et al. 1993). The Shaikh et al. (1993) study employed acute exposures. Strain differences in carcinogenic effects have also been reported for chronic exposures of subcutaneously administered cadmium chloride in male DBA and NFS mice. DBA mice developed lymphomas, while NFS mice developed hepatocellular adenomas and carcinomas, and sarcomas at the injection site. Both strains developed nonneoplastic testicular lesions (fibrosis and mineralization) (Waalkes and Rhem 1994).

Metal-metal interactions are also an important factor in cadmium kinetics and toxicity, and organ specific metal concentrations and metabolism can differ among species. It is thought that further development of PBPK/PD models will assist in addressing these differences and in extrapolating the animal data to support risk assessments in humans.

2.5 RELEVANCE TO PUBLIC HEALTH

Overview. Since the early 1950s, when the hazards of occupational cadmium exposure were recognized (Friberg 1950), a large amount of information has been generated concerning the toxic effects of cadmium exposure. The toxicological properties of cadmium are similar in humans and animals and, as a consequence, rats, mice, rabbits, and monkeys may all provide suitable models for experimental investigation of cadmium toxicity. Toxicological properties are also similar for the several different salts and oxides of cadmium that have been investigated, although differences in absorption and distribution lead to different effect levels. For inhalation exposure, particle size and solubility in biological fluids (in contrast to solubility in water) appear to be the more important determinants of the toxicokinetics (Hirano et al. 1989a, 1989b; Oldiges and Glaser 1986; Rusch et al. 1986). For oral exposure, most experimental studies have used soluble cadmium, which exists as the Cd^{+2} ion regardless of the initial salt. Absorption appears to be similar for cadmium ion and cadmium complexed with proteins in food, except for a few specific types of foods such as Bluff oysters and seal meat (see Section 2.3.1.2). Also, poorly soluble cadmium pigments may be absorbed to a lesser extent than soluble cadmium ion (ILZRO 1977; Oldiges and Glaser 1986).

Cadmium is a cumulative toxicant, and the human exposure conditions of most concern are long-term exposure to elevated levels in the diet. For populations surrounding hazardous waste sites, increased dietary consumption could occur from cadmium-contaminated dust on food or hands, from garden vegetables or fruit grown in cadmium-contaminated soil, and from cadmium-contaminated water used for drinking or garden irrigation. Fugitive dust emissions from cadmium-contaminated soil would expose such populations by the inhalation route. Measurement of cadmium in air, soil, drinking water, and groundwater at these sites is necessary to predict whether adverse health effects may occur. There presently is not enough information to judge the potential absorption or toxicity of cadmium from a dermal exposure. The remainder of this section discusses the toxicity of cadmium exposure for important health effects end

points. Issues relevant to children are explicitly discussed in Sections 2.6, Children's Susceptibility, and 5.6, Exposures of Children.

Minimal Risk Levels for Cadmium.

A minimal risk level (MRL) is defined as "an estimate of the daily human exposure to a substance that is likely to be without appreciable risk of noncancer adverse health effects over a specified duration of exposure." No MRLs have been derived for inhalation exposure to cadmium. An MRL for cadmium has been derived for a chronic oral exposure.

Inhalation MRLs.

No MRLs have been derived for inhalation exposure to cadmium.

Oral MRLs.

- An MRL of 0.0002 mg/kg/day has been derived for a chronic-duration oral exposure (365 days or more) to cadmium.

The oral MRL is based on a lifetime accumulated threshold of 2,000 mg of cadmium from dietary sources. This threshold is associated with an increased incidence of proteinuria identified in residents of cadmium polluted areas of Japan (Nogawa et al. 1989). Using an uncertainty factor of 10 for variability in the human population, an MRL of 0.0002 mg/kg/day is derived based on a NOAEL of 0.0021 mg/kg/day. The current average dietary intake of adult Americans is approximately 0.0004 mg/kg/day (Gartrell et al. 1986); and smokers receive about an equal amount from cigarettes (Nordberg et al. 1985). This indicates that Americans currently do not have a large margin of safety with respect to cadmium intake, This interpretation is consistent with studies showing peak kidney cadmium concentrations in North American adults of 20 μg/g wet tissue weight (wet weight) in nonsmokers and 40 μg/g wet weight in smokers (Chung et al. 1986). The level in smokers is only a factor of 5 less than the critical concentration of 200 μg/g wet weight for renal damage in occupationally exposed workers (Roels et al. 1983). A recent large-scale epidemiologic study in Belgium (Buchet et al. 1990) suggests that the critical concentration may be lower (approximately 50 μg/g wet weight in members of the general population, and that 10% of the population of Belgium may exhibit early signs of cadmium-induced renal changes (proteinuria and increased calcium excretion). Taken together, these results suggest that current cadmium exposures, primarily from the diet

and smoking, would have to be lowered significantly before protection from renal damage could be assured for all members of the population.

Alternative methods of deriving an MRL based on the benchmark dose approach and pharmacokinetic modeling for cadmium (Clewell et al. 1997; Crump 1995) have been investigated by the K.S. Crump Group and the results presented in a special report prepared for ATSDR (Crump 1998). Crump (1998) used the Nogawa et al. (1989) end point of kidney dysfunction based upon abnormal urinary β_2-microglobulin and creatinine levels, and the percent response data was converted to quanta1 response rates. The quanta1 end points were then modeled using Weibull or polynomial models. Benchmark dose levels ($BMDL_{10}$s) were derived for the 95% lower bound on the estimated benchmark dose (BMD_{10}) that corresponded to a 10% extra risk. Separate BMDs were estimated for males and females using the two models (Weibull and polynomial). Cumulative exposure levels in mg/kg were converted to mg/kg/day by dividing by 70 years of environmental exposure and 365 days/year resulting in BMDLlos of 0.00075-0.0013 mg/kg/day. Dividing by an uncertainty factor of 10 for human variability, the resulting MRLs would be 0.000075-0.00013 mg/kg/day, a factor of 1.5-3 times lower than the current MRL of 0.0002 mg/kg/day (Crump 1998).

A BMD could not be derived from the data of Buchet et al. (1990) because only very broadly grouped data were reported (Crump 1998). However, a modification of a pharmacokinetic model developed by Oberdorster (1990) was used to calculate the lifetime daily oral intake of cadmium that would result in a urinary excretion of 2.7 μg Cd/day. Based upon this pharmacokinetic modeling approach, and assuming a half-life of 20 years for cadmium excretion from the body, a urinary cadmium level of 2.7 μg Cd/day corresponding to a daily oral intake of 0.84 μg/kg body weight/day was derived. This estimate assumes that all cadmium intake is via the oral route. The 0.84 μg/kg/day estimate, based upon the Buchet et al. (1990) data, represents a LOAEL (i.e., the Buchet et al. analysis is a best estimate of the critical cadmium concentration in the kidney). An uncertainty factor for interindividual variability was not considered necessary because of the large size of the population in the Buchet et al. (1990) study. Using an uncertainty factor of 3 for a minimal LOAEL an MRL of 0.0003 mg/kg/day was derived, which is a factor of 1.5 times greater than the current MRL based on the Nogawa et al. (1989) study.

Death. High levels of exposure to cadmium by the inhalation or oral routes can cause death in humans or animals (Andersen et al. 1988; Barrett et al. 1947; Beton et al. 1966; Buckler et al. 1986; Lucas et al. 1980; Patwardhan and Finckh 1976; Seidal et al. 1993). Inhalation of a lethal dose of cadmium can occur without signs of acute distress during exposure (Beton et al. 1966). The cause of death following inhalation exposure is pulmonary failure due to excessive pulmonary edema, in conjunction with other signs of pulmonary distress and chemical pneumonitis. High oral doses of cadmium induce vomiting; massive fluid imbalance; and widespread gastrointestinal, liver, and other organ damage (Buckler et al. 1986; Wisniewska-Knypl et al. 1971). No accidental oral exposures in humans are known to have caused death (Frant and Kleeman 1941; Shipman 1986). These effects are mainly due to the destruction of cell membranes at the point of entry (the lung for inhalation exposure and the gastrointestinal tract for oral exposure). Parenteral administration of cadmium can also cause death, usually as the result of liver destruction (Goering and Klaassen 1984a, 1984b, 1984c). Environmental levels of cadmium are unlikely to be high enough to cause acute lethality by the inhalation or oral routes, and no studies were found that report such an event.

Systemic Effects.

Respiratory Effects. Acute inhalation exposure to cadmium at concentrations above about 5 mg/m^3 may cause destruction of lung epithelial cells, resulting in pulmonary edema, tracheobronchitis, and pneumonitis in both humans and animals (Beton et al. 1966; Greenspan et al. 1988; Grose et al. 1987; Snider et al. 1973). A single, high-level cadmium exposure can result in long-term impairment of lung function (Beton et al. 1966; Dervan and Hayes 1979; Townshend 1982). At the cellular level, catalase, superoxide dismutase, non-protein sulfhydryl, glucose-6-phosphate dehydrogenase, and glutathione peroxidase are decreased in response to cadmium lung insults. The respiratory response to cadmium is similar to the response seen with other agents that produce oxidative damage (Boudreau et al. 1989). There typically is an alveolar pneumocyte type 2 cell hyperplasia in response to type 1 cell damage and necrosis. The type 2 cell hyperplasia is typically measured with biochemical and cytological assays of bronchoalveolar lavage fluid (Boudreau et al. 1989). Alveolar macrophages are also mobilized in the lung (Driscoll et al. 1992). Longer-term inhalation exposure at lower levels also leads to decreased lung function and emphysema (Cortona et al. 1992; Davison et al. 1988; Glaser et al. 1986; Leduc et al. 1993). Some tolerance to cadmium-induced lung irritation develops in exposed humans (Barnhart and Rosenstock 1984) and animals (Hart et al. 1989a), and respiratory function may recover after cessation of cadmium exposure (Chan et al.

1988). Another effect of long-term inhalation cadmium exposure is damage to the olfactory function (Rose et al. 1992). Lung damage has also been seen in a few studies of oral cadmium exposure in rats (Borzelleca et al. 1989; Miller et al. 1974b; Petering et al. 1979) but the lung effects are likely to be related to liver or kidney damage and subsequent changes in cellular metabolism. Nonoccupational exposure to cadmium is unlikely to be high enough to cause significant respiratory effects.

Cardiovascular Effects. Conflicting evidence has been obtained in both human and animal studies for the effect of cadmium exposure on the cardiovascular system. In some studies on rats, rabbits, and monkeys, cadmium exposure was shown to increase blood pressure (Akahori et al. 1994; Boscolo and Carmignani 1986; Kopp et al. 1982), or to cause cardiac lesions (Jamall et al. 1989). However, studies of exposed humans have found positive (Geiger et al. 1989) negative (Kagamimori et al. 1986) and no (Cummins et al. 1980) association between cadmium exposure and hypertension. This suggests that if cadmium does affect blood pressure, the magnitude of the effect is small compared to other determinants of hypertension. Death rates for cardiovascular disease do not appear to be elevated in populations exposed to cadmium by inhalation or in the diet (Kazantzis et al. 1988; Shigematsu 1984). Overall, the weight of evidence suggests that cardiovascular effects are not a sensitive end point indicator for cadmium toxicity.

Gastrointestinal Effects. The gastrointestinal tract is the target organ for high-level, acute, oral exposure to cadmium in both humans and animals (Andersen et al. 1988; Borzelleca et al. 1989; Frant and Kleeman 1941; Shipman 1986), due to direct irritation of the gastric epithelium. The main symptoms following ingestion of cadmium at doses above about 0.07 mg/kg in humans are nausea, vomiting, and abdominal pain (Nordberg et al. 1973). Gastrointestinal toxicity is not observed in humans or animals after lower levels of oral exposure or after inhalation exposure to cadmium, indicating that gastrointestinal effects are not likely to occur from environmental exposures to cadmium.

Hemtological Effects. Both oral and inhalation exposure to cadmium can cause anemia in humans and animals (Bernard et al. 1979; Friberg 1950; Groten et al. 1990; Kagamimori et al. 1986; Kozlowska et al. 1993; Pleasants et al. 1992, 1993). Oral exposure to cadmium has been shown to reduce uptake of iron from the diet in animals (Hays and Margaretten 198.5; Kelman et al. 1978; Sakata et al. 1988). It is likely that cadmium transported to the gastrointestinal system from the lung following inhalation exposure would also reduce iron absorption. Therefore, anemia induced by inhalation exposure to cadmium is likely to be caused by reduced iron absorption. Those studies of humans exposed to cadmium by inhalation or in the diet that have not found anemia (Chan et al. 1988; Davison et al. 1988; Roels et al. 1981a; Shiwen et al.

1990) may have examined populations with dietary iron intakes adequate to compensate for reduced absorption. Cadmium-induced anemia is unlikely to be of concern for general population exposure.

Musculoskeletal Effects. Prolonged inhalation or ingestion exposure of humans to cadmium at levels causing renal dysfunction can lead to painful and debilitating bone disease in individuals with risk factors such as poor nutrition (Kazantzis 1979; Shigematsu 1984). Evidence from both human and animal studies suggests that lower-level chronic exposure to cadmium causes alternations in renal metabolism of vitamin D, which then may cause milder bone effects (osteoporosis) (Blainey et al. 1980; Kido et al. 1990a; Nogawa et al. 1987, 1990). These effects may be compounded by loss of calcium and phosphate with more severe renal damage, leading to osteomalacia (Kazantzis 1979; Shigematsu 1984). Some studies in mice have found measurable effects in bone prior to development of proteinuria or histologic kidney lesions (Bhattacharyya et al. 1988c; Ogoshi et al. 1989; Watanabe et al. 1986). A recent large-scale cohort study in Belgium found that increased urinary calcium excretion was significantly associated with urinary cadmium levels, an index of kidney cadmium burden (Buchet et al. 1990). This evidence suggests that either cadmium may have a direct effect on bone at levels lower than those causing kidney damage, or that interference with vitamin D metabolism in the proximal tubule may be a more sensitive indicator of cadmium-induced renal damage than proteinuria.

Hepatic Effects. Cadmium accumulates in the liver following inhalation or oral exposure in humans (Lauwerys et al. 1984; Roels et al. 198lb), but there is little evidence for liver damage in humans exposed to cadmium (Nishino et al. 1988). Exposure to cadmium can cause liver damage in animals (necrosis of hepatocytes, metabolic changes, membrane peroxidation), but generally only after high levels of exposure (Andersen et al. 1988; Groten et al. 1990; Kotsonis and Klaassen 1977, 1978). Decreased relative liver weight to body weight ratios have also been reported in male rats, in addition to slightly lower plasma cholesterol and triglyceride levels in monkeys (Akahori et al. 1994; Kozlowska et al. 1993). The resistance of the liver to oral and inhalation cadmium toxicity is apparently due to its ability to synthesize sufficient quantities of metallothionein to sequester all accumulated cadmium (Kotsonis and Klaassen 1978). When cadmium exposure is by injection, a high concentration of cadmium ion that is not bound to albumin or metallothionein reaches the liver, causing hepatic necrosis and even death (Goering and Klaassen 1984a, 1984b, 1984c).

Renal Effects. The kidney is the main target organ for cadmium toxicity following intermediate- or chronic-duration exposure by the inhalation or oral routes, as has been shown by numerous studies in

humans and animals. The first manifestation of kidney damage is decreased reabsorption of filtered lowmolecular- weight proteins, indicating damage to the renal tubules. Production of tubular proteinuria is a relatively specific effect of cadmium on the kidneys and has been observed even following acute parenteral exposure in animals (Wang and Foulkes 1984). This damage has been associated with increased urinary levels of β_2-microglobulin, retinol-binding protein, or other low-molecular-weight proteins (Bernard and Lauwerys 1989). At higher levels or durations of exposure, increased excretion of high-molecular-weight proteins occurs, indicating either glomerular damage (Roels et al. 1989) or severe tubular damage (Mason et al. 1988). Kidney damage, progressing from mild tubular lesions to widespread necrosis, depending on dose, can be demonstrated in animals following parenteral or subcutaneous administration of cadmium salts or cadmium bound to metallothionein (Kjellstrom 1986c).

The sensitivity of the kidney to cadmium is related to the metabolism of cadmium in the body (see Section 2.3.3). Except for extremely high-dose exposure, cadmium exists in the body primarily bound to metallothionein. The CdMT complex is readily filtered at the glomerulus and reabsorbed in the proximal tubule (Foulkes 1978). Within the tubular cells, the metallothionein is degraded in lysosomes and free cadmium is released (Squibb et al. 1984). The synthesis of endogenous metallothionein by the tubular cells is then stimulated, but when the total cadmium content in the renal cortex exceeds approximately 200 μg/g wet weight, the amount of cadmium not bound to metallothionein becomes sufficiently high to cause tubular damage (Roels et al. 1983). Free cadmium ion may inactivate metal-dependent enzymes, activate calmodulin, and/or damage cell membranes through activation of oxygen species (Waalkes and Goering 1990).

Acute exposure to low levels of cadmium bound to metallothionein produced an intracellular renal damage (Squibb et al. 1984), but damage to brush-border membranes of the renal tubule has also been reported from metallothionein-bound cadmium (Suzuki and Cherian 1987) suggesting other toxic mechanisms may be present. Recent studies indicate that the protein portion of CdMT is rapidly degraded after renal uptake of CdMT and that the released Cd is retained in the kidney (Dorian et al. 1992a, 1992b). CdMT has been shown to be more toxic than $CdCl_2$ (Dorian et al. 1995). CdMT renal injury occurred with dosages as low as 0.2 mg Cd/kg, while renal function was unaltered by $CdCl_2$ even at dosages as high as 3 mg Cd/kg. CdMT distributed almost exclusively to the kidney, whereas $CdCl_2$ preferentially distributed to the liver. However, a high concentration of cadmium was also found in the kidneys after $CdCl_2$ administration (i.e., the renal cadmium concentration after administration of a high but nonnephrotoxic dose of $CdCl_2$ was equal to or higher than that obtained after injection of nephrotoxic doses of CdMT). The higher nephrotoxicity of

CdMT appears to result from a higher concentration of cadmium in the target cells compared to a comparable exposure to $CdCl_2$. ZnMT is not only nontoxic to the kidney at a dose as high as 5 μmole MT/kg, but it can also protect against the nephrotoxic effect of CdMT without decreasing renal cadmium concentration (Dorian and Klaassen 1995).

Studies in MT-null mice (Liu et al. 1998) indicate that Cd-induced renal injury is not necessarily mediated through a CdMT complex, but that metallothionein is an important intracellular protein for protection against chronic cadmium nephrotoxicity. Studies in MT-transgenic mice also have demonstrated that higher metallothionein concentrations in tissues of MT-TG mice had no appreciable effects on the concentration of cadmium in tissues compared to controls, except for an exception for MT-TG mice given the highest dose of cadmium (300 μmol Cd/kg, po). The high dose MT-TG mice had twice the tissue cadmium concentration of controls (Liu and Klaassen 1996).

The health significance of the early kidney damage is difficult to assess. The decreased resorption of low molecular-weight proteins is not adverse in and of itself, but may be indicative of increased excretion of other solutes. Deaths from renal failure due to cadmium exposure are rare, but even after cadmium exposure ceases, the renal damage continues to progress (Kido et al. 1990b; Roels et al. 1989). Evidence that cadmium exposure may affect kidney vitamin D metabolism with subsequent disturbances in calcium balance and bone density (Buchet et al. 1990; Kido et al. 1989b; Nogawa et al. 1990) suggests that decreased bone density, particularly in elderly women, may be a significant adverse effect of kidney cadmium accumulation.

Dermal Effects. Based on the lack of reported effects among workers occupationally exposed to fairly high concentrations of cadmium dust, cadmium appears to have relatively low dermal toxicity. However, few studies have specifically examined the dermal toxicity of cadmium exposure. Scant information is available on the *in vivo* percutaneous absorption of the different forms of cadmium, although it is believed that very little of any chemical form of cadmium is absorbed through the skin to pose serious health risks. Cadmium binding to soil components and differences in partition coefficients significantly reduces the overall availability and percutaneous absorption of cadmium.

Ocular Effects. Based on the lack of reported effects among workers occupationally exposed to fairly high concentrations of cadmium dust, cadmium appears to have relatively low ocular toxicity. However, few studies have specifically examined the ocular toxicity of cadmium exposure.

Body Weight Effects. Inhaling cadmium has not been shown to affect body weight in humans, but high exposures in animals have significantly reduced body weights. Acute exposures to cadmium in the 4-7 mg Cd/m^3 range have caused significant reductions of body weight in male rats (Buckley and Bassett 1978b; Bus et al. 1978; Grose et al. 1987). No effect levels for acute exposures have been reported at <0.5 mg Cd/m^3 (Grose et al. 1987; Klimisch 1993), except for the less soluble pigments like cadmium sulfide and cadmium selenium sulfide where much higher levels of 99 mg Cd/m^3 for 2 hours and 97 mg Cd/m^3 for 2 hours, respectively, did not result in a decreased body weight (Rusch et al. 1986). Levels of cadmium that significantly reduce rat body weights when administered for an intermediate-duration exposure have been reported for cadmium chloride at around 1 mg Cd/m^3 for female and male rats (Baranski and Sitarek 1987; Kutzman et al. 1986), for cadmium chloride at around 0.394 mg Cd/m^3 for pregnant females (Prigge 1978a), and for cadmium dusts at 0.1 mg Cd/m^3 for female rats (Prigge 1978a). NOAELs have been reported for intermediate exposures to cadmium chloride at 0.394 mg Cd/m^3 for nonpregnant female rats (Prigge 1978a), 0.33 mg Cd/m^3 for rats (Kutzman et al. 1986), and 0.0508 mg Cd/m^3 for male rats (Takenaka et al. 1983). NOAELs have been reported for intermediate exposures to cadmium oxide dust at 0.16 mg Cd/m^3 for female rats (Baranski and Sitarek 1987) and 0.45 mg Cd/m^3 for male rabbits (Grose et al. 1987); and for cadmium sulfide at 1.034 mg Cd/m^3 for male rats (Glaser et al. 1986). A NOAEL for chronic exposure in rats to cadmium sulfate has been reported as 0.95 mg Cd/m^3 (Oldiges and Glaser 1986).

Decreased body weight and decreased rates of growth are common findings in studies where experimental animals are orally exposed to cadmium. Sprague-Dawley rats receiving a single gavage dose of 150 mg/kg cadmium exhibited a 12% decrease in body weight, but 100 mg/kg had no effect (Kotsonis and Klaassen 1977). Daily gavage doses of 15.3 mg/kg over a I0-day period caused a 79% decrease in body weight gain in male Sprague-Dawley rats (Borzelleca et al. 1989). Significant reductions in maternal weight gain have also been reported (Baranski 1985; Machemer and Lorke 1981).

Body weight reductions are also seen in intermediate-duration studies. In general, intermediate-duration doses in feed or drinking water of 3 mg/kg/day or less have either no effect or only a small effect (10-20% decrease) on body weight in rats (Carmignani and Boscolo 1984; Jamall et al. 1989; Loeser and Lorke 1977a; Muller et al. 1988; Ogoshi et al. 1989; Perry et al. 1989; Wilson et al. 1941). Higher doses(4-14 mg/kg/day) had no effect in some studies (Kostial et al. 1993; Kotsonis and Klaassen 1987; Prigge 1978a; Viau et al. 1984) and small effects in others (Cha 1987; Kawamura et al. 1978; Kozlowska et al. 1993). A 29% decrease in maternal weight gain was observed in rats exposed to a high dose of

40 mg/kg/day (Baranski and Sitarek 1987). In mice, a dose of 4.8 mg/kg/day had no effect on maternal weight gain, but a dose of 9.6 mg/kg/day caused a 14% decrease (Webster et al. 1978). A high dose of 232 mg/kg/day in mice caused a 29% decrease in body weight (Waalkes et al. 1993). Beagle dogs were unaffected intraperitoneally mg/kg/day (Loeser and Lorke 1977b), as were rabbits at up to 2.2 mg/kg/day (Boscolo and Carmignani 1986; Tomera and Harakai 1988). A small decrease (11%) was seen in rabbits exposed to 14.9 mg/kg/day for 200 days (Stowe et al. 1972).

A chronic-duration study in rhesus monkeys reported decreased growth rates at 0.4 mg/kg/day, but no effect at 0.12 mg/kg/day (Masaoka et al. 1994). No effect on body weight was seen in rats at up to 4.4 mg/kg/day (Decker et al. 1958; Fingerle et al. 1982; Mangler 1988), but a small effect was seen at 7 mg/kg/day (Waalkes and Rehm 1992). Decreased terminal body weight was observed in mice at a high dose of 57 mg/kg/day (Hays and Margaretten 1985).

No studies were located that reported on changes in body weight after dermal exposure to cadmium.

Metabolic Effects. Hyperthermia and metabolic acidosis were reported in a human male who had ingested 25 mg/kg cadmium as cadmium iodide (Wisniewska-Knypl et al. 1971).

No studies were located regarding metabolic effects in animals after oral or inhalation exposure to cadmium.

Immunological and Lymphoreticular Effects. There is little evidence for immunological effects in people following inhalation exposure to cadmium (Guillard and Lauwerys 1989; Karakaya et al. 1994) and no studies were found regarding immunological effects after oral exposure. Cadmium does not appear to cause contact sensitization after dermal exposure in humans or animals (Rudzki et al. 1988; Wahlberg 1977; Wahlberg and Boman 1979). A wide variety of immunologic alterations have been associated with inhalation or oral cadmium exposure in animals (Blakley 1985, 1986, 1988; Bouley et al. 1982, 1984; Cifone et al. 1989a). Inhalation exposures have been shown to suppress the primary humoral immune response (Graham et al. 1978), to be cytotoxic to spleen lymphocytes (Krzytyniak et al. 1987), to increase spleen weight (Kutzman et al. 1986; Prigge 1978b), to enlarge the thoracic lymph nodes (Oldiges and Glaser 1986), to have no effect on natural killer cell activity or viral induction of interferon in mice (Daniels et al. 1987), and to decrease resistance to bacterial infection while increasing resistance to viral infection (Bouley et al. 1982). Numerous oral exposure studies in rats, mice, and monkeys have established the capability of cadmium to affect the immune system including increasing resistance to viral

infection (Exon et al. 1986), to increase mortality from virally-induced leukemia (Blakley 1986; Malave and de Ruffino 1984), to depress the humoral immune response of 6 week old mice (Blakley 1985), but not of 12-month-old mice (Blakley 1988) to increase the cell-mediated immune response of monkeys (Chopra et al. 1984), to induce anti-nuclear antibodies in mice (Ohsawa et al. 1988) to increase circulating leukocytes in female rats (Borzelleca et al. 1989), to exhibit time-dependent inhibitory and stimulative effects (Cifone et al. 1988b), or to have no effect (Bouley et al. 1984; Stacey et al. 1988a) on natural killer cell activity in rats.

The results are, therefore, conflicting, indicating that cadmium exposure can either stimulate or suppress the immune system, and some observed effects may not be clinically significant. Few studies have directly examined immune function of cadmium-exposed humans and the relevance of the immunologic effects observed in animals to public health is difficult to assess.

Neurological Effects. Neurotoxicity is not generally associated with inhalation exposure to cadmium, although a few studies have specifically looked for neurological effects. Hart et al. (1989b) reported a modest correlation between cadmium exposure and decreased performance on neuropsychologic tests for attention, psychomotor speed, and memory in a small cohort of men exposed to cadmium in the workplace air (average exposure=14.5 years). The small number of men studied makes it difficult to evaluate the significance of this effect. Ijomah et al. (1993) studied an increased prevalence of dementia in elderly people living near an aluminum smelter, but observed no significant difference in the prevalence of dementia between the smelter group and the reference group even though there were significant elevations of plasma and red blood cell aluminum and cadmium concentrations. Rose et al. (1992) reported that the workers chronically exposed to cadmium fumes generated during a brazing operation at sufficient levels to cause renal damage also had impairment in olfactory function.

A few studies have reported an association between environmental cadmium exposure and neuropsychological functioning. These studies used hair cadmium as an index of exposure which has limitations. End points that were affected included verbal IQ in rural Maryland children (Thatcher et al. 1982), acting-out and distractibility in rural Wyoming children (Marlowe et al. 1985), and disruptive behavior in Navy recruits (Struempler et al. 1985). The usefulness of the data from these studies is limited because of the potential confounding effects of lead exposure; lack of control for other possible confounders including home environment, caregiving, and parental IQ levels; and an inadequate

quantification of cadmium exposure. No other human neurological studies on inhaled on ingested cadmium were found.

Acute inhalation exposures to cadmium results in neurotoxicity (i.e., tremors or reduced activity) only at high levels (Rusch et al. 1986). Continuous exposure at lower levels were not neurotoxic (Glaser et al. 1986) although a mid-level dose (1 mg/kg/m^3) did lead to significantly increased relative brain weight (Kutzman et al. 1986). The evidence for neurotoxicity is fairly strong from animal studies with oral exposures. Both a single oral exposure (Kotsonis and Klaassen 1977) and intermediate-duration exposure of adult rats to cadmium have been observed to decrease motor activity significantly (Kotsonis and Klaassen 1978; Nation et al. 1990). Intermediate-duration oral exposure to cadmium has also been reported to cause weakness and muscle atrophy (Sato et al. 1978), to induce aggressive behavior (Baranski and Sitarek 1987), to induce anxiety as manifested by increased passive avoidance behavior (Nation et al. 1984) and by increased ethanol consumption (Nation et al. 1989), and to alter brain biogenic amine content and enzyme activities (Murthy et al. 1989). Doses associated with these effects range from 5 to 40 mg/kg/day cadmium. Degenerative changes in the choroid plexus have been reported in mice exposed to 1.4 mg/kg/day cadmium in drinking water for 22 weeks (Valois and Webster 1989). Peripheral neuropathy has been reported in rats after a 31-month exposure to cadmium in drinking water (Sato et al. 1978). Nerve cell or brain damage following parenteral exposure have also been reported (Arivison 1980; Wong and Klaassen 1982). Four-day-old rats were more susceptible to lesions in the corpus callosum, caudateputamen, and cerebellum than were 8-week old adults following a single subcutaneous injection of cadmium chloride. Postexposure brain lesions and hyperactivity were also evident in newborns at dose levels that produced no such effects in adults (Wong and Klaassen 1982).

In general, however, there is little available human evidence to indicate that cadmium adversely affects the human nervous system at exposures even up to levels that result in renal toxicity.

Reproductive Effects. Evidence is insufficient to determine an association between inhalation exposure to cadmium and reproductive effects in humans. Study results are conflicting, with some showing no effect on male fertility (Gennart et al. 1992), male hormone levels (Mason 1990), sperm density (Noack-Fuller et al. 1992), or semen quality (Saaranen et al. 1989); others found a reduction in sperm number or viability (Xu et al. 1993a). Animal studies with inhalation exposures have reported increased duration of the estrous cycle (Baranski and Sitarek 1987; Tsvetkova 1970), and increased relative testes weight, but no loss in reproductive success (Kutzman et al. 1986).

No studies were located regarding reproductive effects in men or women after oral exposure to cadmium. A number of animal studies have shown adverse reproductive effects to male and female reproductive capacity from oral cadmium exposure. In male rats and mice, acute oral-exposure near-lethal doses (60-100 mg/kg) can cause testicular atrophy and necrosis (Andersen et al. 1988; Bomhard et al. 1987; Borzelleca et al, 1989), and concomitant decreased fertility (Kotsonis and Klaassen 1978). Lower-dose acute exposures of 25-50 mg!kg did not result in reproductive toxicity in male animals (Andersen et al. 1988; Bomhard et al. 1987; Dixon et al. 1976). A number of intermediate-dosing regimens in the 0.25-5 mg/kg/day range resulted in neither testicular histopathologic lesions nor a decrease in male reproductive success (Bomhard et al. 1987; Dixon et al. 1976; Groten et al. 1990; Kotsonis and Klaassen 1978; Loeser and Lorke 1977a, 1977b; Pleasants et al. 1992; Zenick et al. 1982). Some dosing regimens in the 5-14 mg/kg/day range resulted in necrosis and atrophy of seminiferous tubule epithelium (Cha 1987); increased testes weight (Pleasants et al. 1992, 1993); increased prostatic hyperplasias (Waalkes and Rehm 1992); or significantly increased relative testes weight, decreased sperm count and motility, decreased seminiferous tubular diameter, and seminiferous tubular damage (Saxena et al. 1989). Vitamins A and D_3 have been reported to reduce cadmium-related increase in testes weight (Pleasants et al. 1992, 1993).

Higher doses of cadmium are needed to elicit a reproductive toxic response in females than in the males, at least for the effects reported in the literature (Borzelleca et al. 1989). Effects include decreased percentage of fertilized females and percentage of pregnancies (Machemer and Lorke 1981; Sutou et al. 1980) and increased duration of the estrus cycle (Baranski and Sitarek 1987). Reduction in the number of pups born has generally not been seen from female exposures (Petering et al. 1979; Pond and Walker 1975; Sorell and Graziano 1990), but have been observed when both males and females were exposed (Schroeder and Mitchener 1971).

In pregnant albino rats, kidney concentrations of cadmium in the dam exceeded those concentrations found in the liver, while in the pups, renal and liver concentrations were very similar. Body concentrations of cadmium were several orders higher in dams than in the pups (Kostial et al. 1993). Environmental exposures may not be likely to cause reproductive toxicity in exposed humans.

Developmental Effects. There is very little human data on developmental effects from exposure to cadmium, and the studies that do indicate that maternal cadmium exposure may cause decreased birth weight in humans (Hue1 et al. 1984; Tsvetkova 1970) are of limited use because of weaknesses in the study design and lack of control for confounding factors.

In animals, cadmium has been shown to be a developmental toxin by the inhalation, oral, and parenteral routes (Baranski 1985, 1987; Prigge 1978b). Decreased fetal weight and skeletal malformations are produced by relatively high maternal doses due to placental toxicity, interference with fetal metabolism, and damage to the maternal liver (Holt and Webb 1987). Malformations or skeletal effects reported include sirenomelia (fused lower limbs), amelia (absence of one or more limbs), and delayed ossification of the sternum and ribs (Baranski 1985); dysplasia of facial bones and rear limbs, edema, exenteration, cryptorchism, and palatoschisis (Machemer and Lorke 1981); and sharp angulation of the distal third of the tail (Schroeder and Mitchener 1971). Dosing levels were in the 1-20 mg/kg/day range. The most sensitive indicator of developmental toxicity appears to be impaired neurological development. This observation is supported by later studies that noted brain weights of mice dosed orally with cadmium had significantly decreased brain weights, with high levels of cadmium deposits in the brain (Kostial et al. 1993; Xu et al. 1993b). The lowest exposures shown to cause these effects in animals are 0.02 mg/m^3, 5 hours a day, 5 days a week, by inhalation (Baranski 1985) and 0.04 mg/kg/day, 5 days a week orally (Baranski et al. 1983). These exposures are above the chronic NOAELs calculated for renal effects in humans. However, insufficient information is available on developmental toxicity in humans to determine whether developmental effects of cadmium are of concern at levels of environmental exposure.

Genotoxic Effects. Tables 2-6 and 2-7 summarize some of the genotoxicity studies that have been performed for cadmium. Evidence concerning chromosomal aberrations in humans following inhalation (Bauchinger et al. 1976; Deknudt and Leonard 1975; O'Riorden et al. 1978) or oral (Bui et al. 1975; Tang et al. 1990) exposure to cadmium is conflicting. Cadmium does not appear to cause germ cell mutations or chromosomal damage following oral (Sutou et al. 1980; Zenic et al. 1982) or-intraperitoneal (Epstein et al. 1972; Mailhes et al. 1988; Suter 1975) exposure in animals, but does so following subcutaneous exposure (Watanabe and Endo 1982; Watanabe et al. 1979). Positive mutagenicity results have been found in some studies using bacterial cells (Bruce and Heddle 1979; Kanematsu et al. 1980; Mandel and Ryser 1984; Wong 1988), and in most studies using yeast or mammalian cell cultures (Denizeau and Marion 1989; Oberly et al. 1982; Schiestl et al. 1989). Chromosomal aberrations have been found in most studies using

Table 2-6. Genotoxicity of Cadmium *In Vivo*

Species (test system)	End point	Results	Reference
Mammalian cells:			
Inhalation exposure:			
Human lymphocytes	Chromosomal aberrations	+	Deknudt et al. 1973
Human lymphocytes	Chromosomal aberrations	–	Bui et al. 1975
Human lymphocytes	Chromosomal aberrations	+	Deknudt and Leonard 1975
Human lymphocytes	Chromosomal aberrations	+	Bauchinger et al. 1976
Human lymphocytes	Chromosomal aberrations	–	O'Riordan et al. 1978
Human lymphocytes	Chromosomal aberrations	+	Alessio et al. 1993
Oral exposure:			
Mouse bone marrow	Chromosomal aberrations	–	Deknudt and Gerber 1979
Mouse bone marrow	Chromosomal aberrations	+	Mukherjee et al. 1988b
Rat spermatogenesis	Dominant lethal mutations	–	Sutou et al. 1980
Rat spermatogenesis	Dominant lethal mutations	–	Zenick et al. 1982
Human leukocytes	Chromosomal aberrations	+	Shiraishi and Yoshida 1972
Human lymphocytes	Chromosomal aberrations	–	Bui et al. 1975
Human lymphocytes	Chromosomal aberrations	+	Tang et al. 1990
Intraperitoneal exposure:			
Syrian hamster embryo cells	Transformation	+	DiPaulo and Casto 1979
Mouse bone marrow	Chromosomal aberrations	–	Bruce and Heddle 1979
Mouse bone marrow	Chromosomal aberrations	+	Mukherjee et al. 1988a
Mouse bone marrow	Sister chromatid exchanges	+	Mukherjee et al. 1988a
Mouse bone marrow	Micronuclei	(+)	Mukherjee et al. 1988a
Mouse spermatocytes	Chromosomal translocations	–	Gilliavod and Leonard 1975
Mouse spermatozoa	Sperm morphology	–	Bruce and Heddle 1979
Mouse spermatozoa	Sperm morphology	+	Mukherjee et al. 1988a
Mouse spermatogenesis	Dominant lethal mutations	–	Epstein et al. 1972
Mammalian cells:			
Inhalation exposure:			
Human lymphocytes	Chromosomal aberations	+	Deknudt et al. 1973

Table 2-6. Genotoxicity of Cadmium *In Vivo* (continued)

Species (test system)	End point	Results	Reference
Mammalian cells:			
Inhalation exposure:			
Human lymphocytes	Chromosomal aberrations	+	Deknudt et al. 1973
Mouses spermatocytes	Chromosomal aberations	+	Selypes et al. 1992
Mouse spermatogenesis	Dominant lethal mutations	–	Gilliavod and Leonard 1975
Mouse oocytes	Dominant lethal mutations	–	Suter 1975
Mouse oocytes	Aneuploidy	–	Mailhes et al. 1988
Subcutaneous exposure:			
Syrian hamster oocytes	Chromosomal aberrations	+	Watanabe et al. 1979
Mouse blastocysts	Aneuploidy	+	*Watanabe and Endo 1982*
Mouse bone marrow	Sister chromatid exchanges	–	Nayak et al. 1989
Mouse fetal liver and lung cells	Sister chromatid exchanges	–	Nayak et al. 1989

+ = positive result; – = negative result; (+) = weakly positive result

Table 2-7. Genotoxicity of Cadmium *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Prokaryotic organisms:				
Bacillus subtilis	DNA repair	No data	(+)	Nishioka 1975
B. subtilis	DNA repair	No data	(+)	Kanematsu et al. 1980
Salmonella typhimurium (plate incorporation)	Gene mutation	–	–	Bruce and Heddle 1979
S. typhimurium (liquid suspension)	Gene mutation	–	–	Milvy and Kay 1978
S. typhimurium (liquid suspension)	Gene mutation	No data	(+)	Mandel and Ryser 1984
S. typhimurium (plate incorporation)	Gene mutation	–	+	Wong 1988
Eukaryotic organisms:				
Yeast:				
Saccharomyces cerevisiae	Gene mutation	No data	+	Putrament et al. 1977
S. cerevisiae	Intrachromosomal recombination	No data	+	Schiestl et al. 1989
Insects:				
Drosophila melanogaster	Sex-linked recessive lethal mutations	No data	–	Inoue and Watanabe 1978
D. melanogaster	Dominant lethal mutations	No data	+	Vasudev and Krishnamurthy 1979
D. melanogaster	Nondisjunction	No data	–	Ramel and Magnusson 1979
Mammalian cells:				
Mouse lymphoma L5178Y thymidine kinase locus	Gene mutation	No data	(+)	Amacher and Paillet 1980

Table 2-7. Genotoxicity of Cadmium *In Vitro* (continued)

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Mouse lymphoma L5178Y thymidine kinase locus	Gene mutation	No data	+	Oberly et al. 1982
Chinese hamster ovary Hy cells	Chromosomal aberration	No data	+	Rohr and Bauchinger 1976
Chinese hamster ovary CHO cells	Chromosomal aberration	No data	+	Deaven and Campbell 1980
Syrian hamster embryo cells	Transformation	No data	+	Casto et al. 1979
Rat ventral prostate cells	Transformation	No data	+	Terracio and Nachtigal 1988
Rat hepatocytes	Unscheduled DNA synthesis	No data	+	Denizeau and Marion 1989
Human blood lymphocytes	Chromosomal aberration	No data	–	Paton and Allison 1972
Human blood lymphocytes	Chromosomal aberration	No data	+	Shiraishi et al. 1972
Human blood lymphocytes	Chromosomal aberration	No data	–	Deknudt and Deminatti 1978
Human blood lymphocytes	Chromosomal aberration	No data	(+)	Gasiorek and Bauchinger 1981
Human blood lymphocytes	Sister chromatid exchanges	No data	–	Bassendowska-Karska and Zawadzka-Kos 1987
Human blood lymphocytes	Sister chromatid exchanges	No data	–	Avitabile et al. 1993
Human blood lymphocytes	Sister chromatid exchanges	No data	–	Avitabile et al. 1993
Human blood lymphocytes	Sister chromatid exchanges	No data	–	Avitabile et al. 1993

(+) = weakly positive result; – = negative result; + = positive result; DNA = deoxyribonucleic acid

cadmium treatment of mammalian cells (Deaven and Campbell 1980; Rohr and Bauchinger 1976) and in some studies using human lymphocytes in culture (Gasiorek and Bauchinger 1981; Shirashi and Yoshida 1972), and in bone marrow cells following intraperitoneal (Mukherjee et al. 1988a) and oral (Mukherjee et al. 1988b) exposure in mice. Overall, cadmium appears to have the capability of altering genetic material, particularly chromosomes in mammalian cells, but germ cells appear to be protected except at high acute parenteral doses.

Cancer. The relationship between occupational exposure to cadmium and increased risk of cancer (specifically lung and prostate cancer) has been explored in a number of epidemiologic studies. For inhalation exposures, the results of epidemiology studies that evaluated cadmium's effects on increased lung cancer are conflicting. Many of the studies had inadequate controls for confounding factors such as co-exposure with other metal carcinogens and smoking, and there is only a small number of lung cancer mortality cases in the only U.S. cohort studied. Overall, however, the results provide little evidence of an increased risk of lung cancer in humans following prolonged inhalation exposure to cadmium. For prostate cancer, the initial studies in European worker populations exposed to cadmium indicated an elevation in prostate cancer (Kipling and Waterhouse 1967; Kjellstrom et al. 1979; Lemen et al. 1976), but subsequent investigations found either no increases in prostate cancer or increases that were not statistically significant (Elinder et al. 1985; Kazantzis et al. 1988; Sorahan 1987; Thun et al. 1985). Based on an analysis of the mortality data from a 5-year update of the cohort from 17 plants in England, and a review of the other epidemiological evidence, Kazantzis et al. (1992) concluded that cadmium does not appear to act as a prostatic carcinogen.

Studies of occupationally exposed cohorts in countries other than the United States have found some increases in lung cancer, but no clear relationship between level and duration of cadmium exposure and increased risk of lung cancer. Cigarette smoking was also a confounding factor. These cohorts included workers from an English zinc-lead-cadmium smelter (Ades and Kazantzis 1988), from 17 different manufacturing or processing facilities involving cadmium in England (Kazantzis et al. 1988), from a nickel-cadmium battery plant in Sweden (Elinder et al. 1985c), and from a nickel-cadmium battery plant in England (Sorahan 1987). The most recent report comes from Sorahan et al. (1995) who studied mortality rates (lung cancer and nonmalignant respiratory diseases) in 347 copper cadmium alloy workers in the United Kingdom. The authors present results that are consistent with the hypothesis that exposure to cadmium oxide fume increases risk of mortality from chronic non-malignant diseases of the respiratory

system, but that do not support the hypothesis that exposure increases the risks of mortality for lung cancer.

An increased risk of lung cancer from cadmium exposure was reported in studies on the only U.S. cohort (workers in a cadmium recovery plant in Globe, Colorado) (Thun et al. 1985, Stayner et al. 1992), but subsequent studies have attributed the increase to either arsenic exposure and/or smoking (Lamm et al. 1992, 1994; Sorahan et al. 1997). These studies and the conflicting results are discussed in more detail below.

A statistically significant, 2-8-fold excess risk of lung cancer was reported in the highest exposure group (cumulative exposures >8 years x mg/m^3), and the dose-response trend over the three exposure groups was highly significant (Thun et al. 1985). Confounding factors included possible exposure to the heavy metals, arsenic (Thun et al. 1989; Kazantzis et al. 1992) and nickel (Sorahan 1987), which are known human lung carcinogens. The data for the U.S. cohort supported an analysis that controlled for the effects of smoking.

Stayner et al. (1992) used data from a retrospective study on lung cancer mortality in the U.S. to further analyze the lung cancer risk associated with cadmium exposure in the U.S. cohort. The analysis controlled for smoking and for ethnicity (i.e., Hispanic and non-Hispanic workers). Lung cancer mortality rates are lower for Hispanics compared to non-Hispanics. Lung cancer mortality was significantly elevated among non-Hispanics and less than expected among Hispanics (as would be predicted from the use of the white male referent rate). The lung cancer SMR increased with cumulative cadmium exposure and was nearly significant for the entire cohort (SMR=149, 95% CI=95, 222; p=0.076, two-tails). The SMR was significantly elevated in the highest exposure group (>2,921 mg-days/m^3) for the combined cohort (SMR=272, 95% CI=123, 513), and for the three highest exposure groups for the non-Hispanic groups. A significant excess of lung cancer mortality was also observed among workers in the longest time-since-firstexposure category (>20 years) for the combined cohort (SMR=161, 95% CI=l00, 248) and for non-Hispanics (SMR=233, 95% CI=141, 365). A statistically significant dose-response relationship was evident in nearly all of the regression models evaluated. Based on this analysis, the lifetime excess of lung cancer at the previous OSHA standard for cadmium fume of 100 μg/m^3 would be approximately 50-111 lung cancer deaths per 1,000 workers exposed to cadmium for a working lifetime (45 years). At the current OSHA standard of 5 μg/m^3 (OSHA 1992) the lifetime risk of lung cancer was predicted to be approximately 2.6-6 lung cancer deaths per 1,000 workers exposed to cadmium for 45 years (Stayner et al. 1992).

Stayner et al. (1992) also performed an indirect assessment of confounding effects of exposure to arsenic. The analysis indicated that there was no significant effect on lung cancer mortality from cumulative cadmium exposure because of year of hire; in fact, the authors report that their dose-response analysis demonstrated a greater dose-response relationship for workers hired after 1939.

Lamm et al. (1992, 1994) used nearly the same data set for the U.S. cohort as Stayner et al. (1992) in a nested case-control analysis that used the period of hire as a surrogate for arsenic exposure. Based on this analysis, Lamm et al. (1992, 1994) reported no residual association of lung cancer with cadmium in the Globe, Colorado, cohort; they reported that cases were more than eight times more likely to have been cigarette smokers than were their controls. They concluded that arsenic exposure and cigarette smoking were the major determinants of lung cancer risk, not cadmium exposure.

The reasons for these conflicting conclusions based on the same cohort data are unclear. Doll (1992) suggested some possible reasons including: (1) that the total number of cases was small (n=25) and that only 21 of these cases were included in both studies (i.e., each study included some cases that were not included in the other study); (2) that Stayner et al. (1992) used national rather than regional mortality rates; (3) that the Lamm et al. (1992, 1994) control series was overmatched, although the matching by date of hire was necessary to control for arsenic exposure; and (4) that there are some concerns about the validity (i.e., biological relevance) of the dose-response-models used by Stayner et al. (1992). In a response to Doll (1992), Stayner et al. (1993) reported that use of regional mortality rates would increase rather than decrease support for their conclusion, and that the nested case-control analysis of Lamm et al. (1992) used overmatched controls. Stayner et al. (1993) provide additional analyses including the use of the Armitage-Doll multistage model to support the conclusion of an increased risk of cancer from cadmium exposure.

Sorahan and Lancashire (1994) subsequently raised concerns about inconsistencies and inaccuracies in the NIOSH job history data used in these studies on the U.S. cohort. Sorahan and Lancashire (1997) then conducted further analyses, based on detailed job histories extracted from time sheet records, to better resolve the potential confounding affects of arsenic. After adjustment for age attained, year of hire, and Hispanic ethnicity; Sorahan and Lancashire (1997) report a significant positive trend ($p<0.05$) between cumulative exposure to cadmium and risks of mortality from lung cancer. However, when the exposure to cadmium was evaluated with or without concurrent exposure to arsenic, a significant trend for lung cancer was only found for exposure to cadmium received in the presence of arsenic trioxide. Since there were only 21 deaths from lung cancer, Sorahan and Lancashire (1997) state that it is impossible to determine which

of the following three hypotheses is the correct one: (1) cadmium oxide in the presence of arsenic trioxide is a human lung carcinogen, (2) cadmium oxide and arsenic trioxide are human lung carcinogens and cadmium sulphate and cadmium sulphide are not (i.e., cadmium sulphate and cadmium sulphide were the main cadmium compounds of exposure when arsenic was not present), or (3) arsenic trioxide is a human carcinogen and the three cadmium compounds are not carcinogenic.

There were no human studies found (occupational or environmental exposures) that associated an increase in cancer with oral exposure in humans. Available epidemiologic studies, however, had no reliable estimates of individual doses (Bako et al. 1982; Inskip and Beral 1982; Lauwerys and De Wals 1981; Nakagawa et al. 1987), and so had limited sensitivity to detect a carcinogenic effect.

The controversy about the adequacy of the human cancer data for cadmium is reflected in the cancer classifications from different agencies. The Environmental Protection Agency EPA has classified cadmium as a probable human carcinogen by inhalation (Group Bl), based on its assessment of limited evidence of an increase in lung cancer in humans (Thun et al. 1985) and sufficient evidence of lung cancer in rats (IRIS 1996; Takenaka et al. 1983). EPA has calculated an inhalation unit risk (the risk corresponding to lifetime exposure to 1 $\mu g/m^3$) of $1.8x10^{-3}$ (IRIS 1996). The National Toxicology Program (NTP) has classified cadmium and certain cadmium compounds as substances that are reasonably anticipated to be carcinogens, based on an assessment of limited evidence for carcinogenicity from studies in humans and sufficient evidence for carcinogenicity in humans (NTP 1994). In contrast, the International Agency for Research for Research on Cancer (IARC) has classified cadmium as carcinogenic to humans (Group 1) based on an assessment of sufficient evidence for carcinogenicity in both human and animal studies (IARC 1993).

Strong evidence from animal studies exists that cadmium inhalation can cause lung cancer, but only in rats. Inhalation exposure of rats to various chemical forms of cadmium for 18 months caused lung tumors during the subsequent 13-month follow-up period (Oldiges et al. 1989; Takenaka et al. 1983). No other type of tumor showed any significant dose-response trend (Takenaka et al. 1983). Mice similarly exposed had only marginally significant elevations in lung cancer rate, but the rate of lung cancers in control mice was high and variable (Heinrich et al. 1989). No evidence for lung carcinogenicity in hamsters was found, possibly due to lung damage and subsequent decreased survival at high doses (Heinrich et al. 1989). Intratracheal instillation of up to three doses of cadmium oxide caused no increase in lung tumors in male rats, but did increase the incidence of mammary fibroadenomas (Sanders and Mahaffey 1984). The increase was significant when all dose groups were pooled (Sanders and Mahaffey 1984).

All but one of the animal studies show no cadmium-related increase in cancer from oral exposure. The early animal carcinogenicity experiments had limited sensitivity because the maximum doses used were 1 mg/kg/day in mice (Schroeder et al. 1964) and 2.5 mg/kg/day in rats (Loser 1980). Doses up to 6.5 mg/kg/day in mice (Bhattacharyya et al. 1988b) and 12.5 mg/kg/day in rats (Bornhard et al. 1984) have been used in noncancer chronic-duration animal studies, so the doses used in the oral carcinogenicity studies were clearly below the maximum tolerated dose. More recently, Waalkes and Rehm (1992) reported that cadmium in a zinc controlled diet increased prostatic proliferative lesions (both hyperplasias and adenomas), leukemia, and testicular tumors in rats. The overall incidence for tumors of the prostate, testes, and hematopoietic system decreased in zinc-deficient rats. These results indicate that dietary zinc deficiency has complex, apparently inhibitory, effects on cadmium carcinogenesis by the oral route.

Waalkes et al. (1993) also report that cadmium can effectively “impair” tumor formation in the lungs and liver of male $B6C3F_1$ mice given a tumor promotor (n-nitrosodiethylamine) and exposed to a relatively high level of cadmium (232 mg/kg/day) via the drinking water for up to 48 weeks. Cadmium appeared to be able to destroy existing preneoplastic and/or tumor cells (adenomas) selectively. The mechanism may involve a reduced activity and responsiveness of the metallothionein system in transformed liver cells.

Injection of cadmium into the skin or muscle causes tumors in rats, primarily at the site of injection and in the testes (Bornhard et al. 1987; Poirer et al. 1983; Waalkes et al. 1989). The induction of testicular tumors following cadmium injection appears to be directly related to the testicular degeneration (Bomhard et al. 1987). When rat testes do not experience degeneration following cadmium injection, either because the cadmium injection is intramuscular or because the testes are protected by subcutaneous injection of zinc, no testicular tumors occur (Waalkes et al. 1989). A consequence of testicular degeneration caused by subcutaneous cadmium injection is atrophy of prostatic tissue, but when testicular degeneration does not occur, the prostate does not atrophy and prostatic tumors develop (Waalkes et al. 1989). This latter finding indicates that systemic exposure to cadmium may induce prostate tumors, but further suggests that these tumors can only be detected when cadmium-induced testicular degeneration is prevented.

The relevance of carcinogenicity experiments using parental exposure is uncertain because of the substantial differences in the toxicity and toxicokinetics of cadmium after oral or inhalation exposure compared to the toxicity and toxicokinetics of injected cadmium ion (Goering and Klaassen 1984a, 1984b, 1984; Kotsonis and Klaassen 1977, 1978). Strain differences in carcinogenic effects have also been reported for chronic exposures of subcutaneously administered cadmium chloride in male DBA and NFS

mice. DBA mice developed lymphomas, while NFS mice developed hepatocellular adenomas and carcinomas, and sarcomas at the injection site. Both strains developed nonneoplastic testicular lesions (fibrosis and mineralization) (Waalkes and Rehm 1994a). Waalkes and Rehm (1994b) also report a cadmium associated increase in hematopoietic tumors, primarily follicular center-cell lymphomas, in BALB/c mice following subcutaneous injection; however, not only was there an effect on the incidence of lung tumors, cadmium suppressed the multiplicity of pulmonary tumors (i.e., the mean number of lung tumors per animal).

Maximilien et al. (1992) raises concerns about the appropriateness of the rat model for cadmium induced lung tumors in humans. This is a serious concern because the strength of the animal data in support of a cadmium dose-response increase in lung tumors from inhalation exposure primarily rests on the rat model. These authors argue that cadmium is a contact carcinogen and that differences in the morphology of the rat respiratory tract result in a deposition pattern and target cell population that are quite different from the deposition pattern and target cell population that would result from human inhalation exposure. Differences between the rat and human clearance rates, speciation at the level of the target cell, and protein transporters (as they relate to solubility and susceptibility) are not well characterized. Data are also presented in support of the hypothesis that cadmium is not an initiator in rats, and that cadmium carcinogenicity in this model may be phenomenon limited to older rats. These concerns merit further investigation.

2.6 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 due to 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 5.6, 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 pre-natal and post-natal 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 and 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 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 the newborn who has a low glomerular filtration rate and has 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 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 while others may decrease susceptibility to the same chemical. For example, the fact that infants breathe more air per kilogram of body weight than adults may be somewhat counterbalanced by their alveoli being less developed, so there is a disproportionately smaller surface area for absorption (NRC 1993).

The health effects seen in children from exposure to toxic levels of cadmium are expected to be similar to the effects seen in adults (i.e., kidney, lung, and intestinal damage depending on the route of exposure).

Because cadmium is a cumulative toxin and has a very long half-time in the body, exposures to children in even low amounts may have long-term adverse consequences. Average cadmium concentrations in the kidney are near zero at birth, and rise roughly linearly with age to a peak (typically around 40-50 μg/g wet weight) between ages 50 and 60, after which kidney concentrations plateau or decline (Chung et al. 1986; Hammer et al. 1973; Lauwerys et al. 1984). Liver cadmium concentrations also begin near zero at birth, increase to typical values of l-2 μg/g wet weight by age 20-25, then increase only slightly thereafter (Chung et al. 1986; Hammer et al. 1973; Lauwerys et al. 1984; Sumino et al. 1975).

A potential for cadmium to have adverse neurological effects is an important consideration. However, only a few studies have reported an association between environmental cadmium exposure and neuro-psychological functioning. End points that were affected included verbal IQ in rural Maryland children (Thatcher et al. 1982), and acting-out and distractibility in rural Wyoming children (Marlowe et al. 1985). The usefulness of the data from these studies is limited, however, because of the potential confounding effects of lead exposure; lack of control for other possible confounders including home environment, caregiving, and parental IQ levels; and because of an inadequate quantification of cadmium exposure (i.e., the studies used hair cadmium as an index of exposure which has some limitations because of potential confounding from exogenous sources).

The human information for developmental effects following exposure to cadmium is very limited. Russian women occupationally exposed to cadmium at concentrations ranging from 0.02 to 35 mg/m^3 had offspring with decreased birth weights but without congenital malformations, compared to unexposed controls (Tsvetkova 1970). However, no association was found between birth weights of offspring and length of maternal cadmium exposure, and no control was made for parity, maternal weight, gestational age, or other factors known to influence birth weight. A nonsignificant decrease in birth weight was found in offspring of women with some occupational exposure to cadmium in France; however, no adverse effects were documented in these newborns (Hue1 et al. 1984). Hue1 et al. (1984) used hair samples to estimate exposure but the usefulness of this data is limited because there were no controls to distinguish between exogenous and endogenous sources. No other human studies were located regarding developmental effects in humans after inhalation exposure to cadmium.

Developmental toxicity from exposure to cadmium is most often reported in animal studies from an oral exposure. Baranski (1985), however, reported developmental toxicity in offspring of female rats exposed to cadmium oxide at 0.02 mg Cd/m^3 for 5 hours a day, 5 days a week, for 4-5 months prior to mating and

during the first 20 days of gestation. The effects reported included delayed ossification, decreased locomotor activity, and impaired reflexes in offspring. Decreases in weight gain, osteogenesis, and viability were also noted at concentrations of 0.16 mg/m^3 (Baranski 1985).

Many studies in rats and mice indicate that cadmium can be fetotoxic from oral exposures prior to and during gestation. This fetotoxicity is most often manifested as reduced fetal or pup weights (Ali et al. 1986; Baranski 1987; Gupta et al. 1993; Kelman et al. 1978; Kostial et al. 1993; Petering et al. 1979; Pond and Walker 1975; Sore11 and Graziano 1990; Sutou et al. 1980; Webster 1978; Whelton et al. 1988), but malformations, primarily of the skeleton, have been found in some studies (Baranski 1985; Machemer and Lorke 1981; Schroeder and Mitchener 1971). Malformations or skeletal effects reported include sirenomelia (fused lower limbs), amelia (absence of one or more limbs), and delayed ossification of the sternum and ribs (Baranski 1985); dysplasia of facial bones and rear limbs, edema, exenteration, cryptorchism, and palatoschisis (Machemer and Lorke 1981); and sharp angulation of the distal third of the tail (Schroeder and Mitchener 1971). Dosing levels were in the l-20 mg/kg/day range.

The most sensitive indicator of developmental toxicity of cadmium in animals appears to be neurobehavioral development. Offspring of female rats orally exposed to cadmium at a dose of 0.04 mg/kg/day prior to and during gestation had reduced exploratory locomotor activity and rotorod performance at age 2 months (Baranski et al. 1983). Pups from dams exposed to 0.7 mg/kg/day during gestation had significant delays in cliff aversion and swimming behavior. Locomotor activity was significantly increased. In post-weaning measurements, locomotor activity was significantly decreased in treated groups at 60 days of age; conditioned avoidance behavior was also significantly decreased when tested at 60 and 90 days of age (Ali et al. 1986).

Nagymajtenyi et al. (1997) also reported behavioral and functional neurotoxicological changes caused by cadmium in a three-generational study in rats. Three consecutive generations of Wistar rats were orally treated by gavage with 3.5, 7.0, or 14.0 mg Cd/kg body weight (as cadmium chloride diluted in distilled water) over the period of pregnancy, lactation, and 8 weeks after weaning. Behavioral (open-field behavior) and electrophysiological (spontaneous and evoked cortical activity, etc.) parameters of male rats from each generation were investigated at the age of 12 weeks. The main behavioral outcomes were increased vertical exploration activity (rearing) and increased exploration of an open-field center. The spontaneous and evoked electrophysiological variables showed dose- and generation-dependent changes (increased frequencies in the electrocorticogram, lengthened latency and duration of evoked potentials, etc.)

signaling a change in neural functions. The results indicate that low-level, multigeneration exposure of rats to inorganic cadmium can affect nervous system function.

Desi et al. (1998) continued the above studies to further evaluate cadmium-associated changes in behavior and neurological function in rats following different dosage regimens during pregnancy. Female Wistar rats were given 3.5, 7.0, or 14.0 mg Cd/kg body weight (cadmium chloride dissolved in distilled water) in three different treatment regimes: days 5-15 of pregnancy; days 5-15 of pregnancy + 4 weeks of lactation; days 5-15 of pregnancy + 4 weeks of lactation followed by the same oral treatment of male rats of the Fl generation for 8 weeks. The behavioral (open-field exploration) and electrophysiological (electrocorticogram, cortical evoked potentials, conduction velocity and refractory periods of a peripheral nerve) parameters of Fl male rats exposed by various treatments were investigated at age 12 weeks. The results indicate that cadmium altered the spontaneous and evoked electrophysiological functions (e.g., increased the frequency of the electrocorticogram, lengthened the latency and duration of evoked potentials, etc.) in a dose- and treatment-time-dependent manner. Only the combination of treatment during prenatal development and the 4-week suckling period resulted in a significant dose-dependent decrease of horizontal and vertical exploratory activity and a significantly lower exploration frequency of the open-field center. The results suggests that low-level pre- and postnatal inorganic cadmium exposure affects the electrophysiological functions and higher order functions of the nervous system.

Gupta et al. (1993) examined the developmental profiles of DNA, RNA, proteins, DNA synthesis, thymidine kinase activity, and concentrations of zinc and cadmium in the brain of neonates from dams exposed to cadmium acetate at 5-6.3 mg/kg/day in drinking water during gestation, and 7-8 mg/kg/day during a 21-day lactation period. Pup brain and body weights were significantly decreased in the cadmium exposed pups on lactation days (Ld) 7-21. Cadmium brain accumulation was significantly increased in exposed pups on Ld 7 and remained at similar levels on Ld 14 and 21. DNA and thymidine kinase brain levels were significantly decreased in treated pups compared with controls on Ld 7, 14, and 21. The toxicological significance of changes in DNA levels and thymidine kinase activity are uncertain.

Xu et al. (1993b) determined lipid peroxide (LPO) concentrations in rat pups in various organs as an index of cadmium toxicity. Male and female Wistar mice were exposed to cadmium in drinking water at 0, 5.7, or 14.25 mg/kg/day for 2 months prior to mating. The pregnant females continued to be exposed during gestation and lactation. Litter size and pup survival rates were unaffected by cadmium. Body weights were not statistically different between the exposed and control groups. In pups, brain weights (at 5.7 and

14.25 mg/kg/day) and liver, kidney, and heart weights (at 14.25 mg/kg/day) were significantly decreased. Although the relative organ weights were lower in the high-dose group, the difference from controls was not statistically significant. LPO concentrations in all organs were significantly increased in pups on Ld 7 at 14.25 mg/kg/day except in the kidney; concentrations in the liver, heart, and brain were 131.5, 156, and 237.4%, respectively, of the concentrations in controls.

In contrast to most of the study results, Saxena et al. (1986) reported no developmental effects from an exposure to 21 mg Cd/kg/day via drinking water during gestation (Gd 0-20). This study evaluated simultaneous exposure to lindane (20 mg lindane/kg via gavage on Gd 6-14) and cadmium acetate in drinking water at doses that individually did not cause maternal or developmental effects. Maternal toxicity (significantly decreased weight gain) and developmental toxicity were only observed in the cadmium plus lindane group. Fetal body weight was significantly decreased; intrauterine death and the rate of skeletal anomalies were significantly increased. Anomalies consisted of decreased ossification, wavy ribs, and scrambled sternebrae.

Cadmium is known to dramatically increase resorption of bone calcium in animals fed calcium deficient diets, resulting in painful bone disorders, including osteomalacia, osteoporosis, and spontaneous and painful bone fractures (an affliction called Itai-Itai or “ouch-ouch” disease). Long-term exposures of cadmium to infants and children would result in the accumulation of cadmium in the bone.

Ogoshi et al. (1989) studied the mechanical strength of femurs of young, adult, and elderly female rats after a 4-week exposure to $CdCl_2$ in drinking water. Young rats (21 days old; strain not specified; N=19-22F) were given $CdCl_2$ at 0, 5, or 10 ppm; adult rats (24 weeks old; strain not specified; N=18-25NS) were given $CdCl_2$ at 0, 10, 20, 40, 80, or 160 ppm (adult rats); elderly rats (1.5 years old; strain not specified; N=25-27NS) were given $CdCl_2$ at or 0, 80, or 160 ppm. At the end of the 4 week exposure, femur compression and bending were evaluated. Young rats had decreased bone strength at both doses tested (5 and 10 ppm), while adult and elderly rats showed no effect up to doses of 160 ppm. Bone strength was correlated with cadmium content of bone but not cadmium content of liver or kidney. Young rats accumulated cadmium in the bones to a much greater extent (100 ng/g dry weight at 5 ppm, 150 ng/g at 10 ppm) then did the adult or elderly rats whose accumulation was roughly comparable and about 65 ng/g at the highest dose of 160 ppm.

Oral cadmium exposure has also been reported to suppress the T-lymphocyte and macrophage dependent humoral immune response of 6-week-old mice against sheep red blood cells (Blakley 1985), but not of 12-month-old mice (Blakley 1988). In 6-week-old mice, Blakley (1985) studied the effect of cadmium chloride on the immune response in female BDF_1 mice (N=22) administered $CdCl_2$ in drinking water for 3 weeks at doses of 0, 5, 10, or 50 μg/mL. Parameters monitored included body weight gain, response of splenic lymphocytes to specific mitogens in the presence or absence of cadmium, humoral response of spleen cells against sheep red blood cells (SRBC) as measured by plaque counts, and kidney cadmium levels. No overt clinical signs, weight gain, or gross pathology were observed following cadmium exposure at these levels. A-dose-response increase in kidney cadmium was observed with concentrations in 0, 5, 10 and 50 ppm groups of 0.17,0.33, 1.02 and 5.98 μg/g wet weight, respectively. A dose-dependent suppression of the immune response of spleen cells to SRBC antigen was observed with a reduction in plaque count of 28.2% in the high dose group. The B-lymphocyte response to SRBC antigen is T lymphocyte dependent and requires the presence of macrophages. Cadmium-induced dysfunction to any or all 3 cell types could lead to the observed suppressed humoral response. To evaluate a potential suppression of the proliferation of T- and B-lymphocytes by cadmium, splenic lymphocytes were exposed to 0, 0, 5, 10, or 50 μg cadmium/ml in conjunction with the known mitogens, concanavalin A for T-lymphocytes, or *Escherichia coli* lipopolysaccharide for B-lymphocytes. Proliferative response from exposure to mitogen was measured as an increase in DNA synthesis. Rather than lessen the proliferative response, T-lymphocyte proliferative response to concanavalin A was not affected by cadmium exposure. Further, the proliferative response of B-lymphocytes to *Escherichia coli* lipopolysaccharide was signif-icantly enhanced by cadmium in a dose-responsive manner. Cadmium alone was, itself, mildly mitogenic, thus cadmium suppression of the primary humoral immune response to SRBC antigen does not appear to result from an impaired lymphocyte proliferative response. Further evaluation is needed, but the author notes that the suppressed humoral response in young mice occurred at relatively low kidney cadmium levels, indicating that the immune system of the young mouse is relatively sensitive to the effects of cadmium.

In contrast to the suppressed humoral response to SRBC antigen observed in 6-week-old mice, Blakley (1988) did not observe a similar response under similar test conditions for 12-month-old mice. The author suggests that “natural” age-related immune system dysfunction masked any cadmium suppressive effect.

Children are most likely to be exposed to cadmium in food or water. Most ingested cadmium passes through the gastrointestinal tract without being absorbed. In adults, only about one-twentieth of the total ingested cadmium (in food or water) is absorbed (McLellan et al. 1978, Rahola et al. 1973). The retention

of cadmium in the gut slowly decreases over a period of l-3 weeks after ingestion in adults (Rahola et al. 1973). The absorption of cadmium in rats depends on age, with measured absorption decreasing from 12 to 5 to 0.5% at 2 hours, 24 hours, and 6 weeks after birth, respectively (Sasser and Jarboe 1977). Sasser and Jarboe (1980) also reported that absorption of cadmium in the gastrointestinal tract of young guinea pigs was 20 fold higher than in adult guinea pigs.

Absorption from the gut appears to take place in two phases, uptake from the lumen into mucosa, then transfer into the circulation. Factors affecting cadmium absorption include metal-metal (e.g., iron, calcium, chromium, magnesium, zinc) and the form of cadmium (i.e., protein or sulfhydryl bound, or ionic) in the food or water. Levels of other metals and proteins can vary with age and physiological status, and affect cadmium kinetics. Animal studies have shown that low levels of iron, calcium, or protein in the diet can increase the amount of cadmium absorbed into the body (Friberg et al. 1974). Increased fat in the diet can also increase cadmium absorption (i.e., probably from the longer residency times for absorption to occur). Cadmium is not well absorbed by the skin (about 0.5%), and there is not a significant risk from skin exposure unless contact with the skin is for long periods of time or at very high levels.

Differences in individual sensitivity to cadmium have not been systematically studied, but based on what is known about cadmium toxicity, inferences can be made. The body store of iron influences cadmium absorption; subjects with low iron stores (assessed by serum ferritin levels) had an average absorption of 8.9%, while those with adequate iron stores had an average absorption of 2.3% (Flanagen et al. 1978). Women with depleted stores of calcium, iron, or other dietary components due to multiple pregnancies and/or dietary deficiencies can be expected to have increased cadmium absorption from the gastrointestinal tract, while oral zinc supplementation has been shown to decrease the oral absorption of cadmium. Children with depleted stores of iron, calcium, or protein may also have increased absorption of cadmium.

Tissue distribution and retention of cadmium differed between 4-day-old rats and 70-day-old adult rats. Cadmium was 3-6 times more concentrated in the newborn spleen, bone, brain, testes, and muscle than in the adult rat 2 hours after an intravenous administration of 1 mg Cd/kg body weight. Liver concentration of metallothionein was 20 times greater in the newborn than in the adult; kidney metallothionein concentrations were comparable, but liver cadmium was only 30% higher and kidney cadmium was 50% higher in the newborn. Nineteen days post-cadmium exposure, the retention of cadmium in the liver, kidney, and lung was similar in both the newborn and the adult rat (Wong and Klaassen 1980a). Goering and Klaassen (1984) report that high levels of metallothionein in 10-day-old rats play an important role in their resistance

to liver damage, presumably by binding and retaining cadmium. However, the tissue distribution data led Wong and Klaassen (1990a) to propose that metallothionein does not play a major role in the tissue distribution and retention of cadmium in the young.

Cadmium can be transferred to offspring in breast milk. Cadmium levels in human milk are 5-l 0% of levels in blood, possibly due to inhibited transfer from blood because of metallothionein binding of cadmium in blood cells (Radisch et al. 1987). In female outbred albino rats exposed to cadmium in drinking water (as $CdCl_2$) at 0 or 4.8 mg/kg/day for 10 weeks (at 4 weeks prior to mating, at 3 weeks of gestation, or 3 weeks into lactation), kidney concentrations exceeded liver concentrations, while in their pups, the renal and liver concentrations were similar at all times during exposure. In pups, both hepatic and renal cadmium concentrations considerably increased only during the second half of the lactation period (Ld 11-21). The cadmium tissue concentrations in dams were several orders higher than in offspring.

Although studies on elimination of cadmium from the tissues of children are not available, the results of studies in animals provide some insight. Most cadmium that is ingested or inhaled and transported to the gut via mucociliary clearance is excreted in the feces. Of the cadmium that is absorbed into the body, most is excreted very slowly, with urinary and fecal excretion being approximately equal (Kjellstrom and Nordberg 1978). Half-times for cadmium in the whole body of mice, rats, rabbits, and monkeys have been calculated to be from several months up to several years (Kjellstrom and Nordberg 1985). Half-times in the slowest phase were from 20 to 50% of the maximum life span of the animal (Kjellstrom and Nordberg 1985). In the human body, the main portion of the cadmium body burden is found in the liver and kidney and in other tissues (particularly muscle, skin, and bone). After reviewing the literature, Kjellstrom and Nordberg (1985) developed a range of half-times from their kinetic model for the human kidney of between 6 and 38 years, and for the human liver of between 4 and 19 years. These high values indicate the persistence of cadmium in the body and the importance of minimizing exposures in children to prevent long-term accumulation and toxicity.

The placenta may act as a partial barrier to fetal exposure to cadmium. Cadmium concentration has been found to be approximately half as high in cord blood as in maternal blood in several studies including both smoking and nonsmoking women (Kuhnert et al. 1982; Lauwerys et al. 1978; Truska et al. 1989). Accumulation of cadmium in the placenta at levels about 10 times higher than maternal blood cadmium concentration has been found in studies of women in Belgium (Roels et al. 1978) and the United States (Kuhnert et al. 1982); however, in a recent study in Czechoslovakia, the concentration of cadmium in the

placenta was found to be less than in either maternal or cord blood (Truska et al. 1989). In mice orally exposed to cadmium during pregnancy, maternal blood, placental, and fetal cadmium concentrations were essentially equal among control animals (with environmental cadmium exposure), but placental concentration increased with cadmium dose much more rapidly than either maternal blood or fetal cadmium concentration (Sore11 and Graziano 1990). Thus, timing and level of cadmium exposure may influence the utake of cadmium by the placenta, perhaps explaining the conflicting human studies.

Of particular importance to the toxicokinetics and toxicity of cadmium is its interaction with the protein metallothionein. Metallothionein is a low-molecular-weight protein, very rich in cysteine, which is capable of binding as many as seven cadmium atoms per molecule and is inducible in most tissues by exposure to cadmium, zinc, and other metals (Waalkes and Goering 1990). Metallothionein binding decreases the toxicity of cadmium (Goyer et al. 1989; Kotsonis and Klaassen 1978). Goyer et al. (1992) localized metallothionein in full-term human placenta and in fetal cells in human placenta. Metallothionein was present in trophoblasts (which facilitate transport of substances entering the placenta from the maternal blood), Hofbauer cells (motile macrophages capable of phagocytosis and protein ingestion), amniotic epithelial cells (fetal derivatives), and decidual cells (endometrial stromal cells that have been transformed under hormonal influence into large pale cells, rich in glycogen). The mechanism by which the placenta transports the essential metals, copper and zinc, while limiting the transport of cadmium is unknown, but may involve the approximately 1,000-fold higher concentration of zinc in the placenta and the higher affinity of cadmium than zinc for metallothionein.

Chan and Cherian (1992) report that pregnancy in Sprague-Dawley rats previously administered cadmium chloride (1.0 mg Cd/kg body weight subcutaneously, daily for 8 days) leads to a mobilization of cadmium from the liver (40% decrease compared to nonpregnant cadmium treated controls) and an increase in the kidneys (60% increase). A similar pattern is seen for metallothionein. Plasma cadmium and metallothionein also increased in the pregnant group. Placental cadmium increased in the cadmium-treated rats ompared to the untreated controls. In this rat model, then, pregnancy resulted in a transfer of hepatic admium and metallothionein via the blood to the kidney and placenta.

2.7 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 (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 cadmium are discussed in Section 2.7.1.

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 cadmium are discussed in Section 2.7.2.

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 2.9, Populations That Are Unusually Susceptible.

2.7.1 Biomarkers Used to Identify or Quantify Exposure to Cadmium

Cadmium levels in blood, urine, feces, liver, kidney, hair, and other tissues have been used as biological indicators of exposure to cadmium. A discussion of the utility and limitations of each for human biomonitoring is provided below.

Blood cadmium levels are principally indicative of recent exposure(s) to cadmium rather than whole body burdens (see Section 2.3) (Ghezzi et al. 1985; Jarup et al. 1988; Lauwerys et al. 1994; Roels et al. 1989). Concentrations of cadmium in blood in normal populations range from about 0.4 to 1.0 μg/L for non-smokers and 1.4-4 μg/L for smokers (Elinder 1985b; Sharma et al. 1982). Environmental exposure can elevate blood cadmium concentration to above 10 μg/L (Kido et al. 1990a, 1990b; Shiwen et al. 1990). Workers occupationally exposed to cadmium by inhalation may have blood cadmium levels ranging up to 50 μg/L (Roels et al. 1981b). Blood concentrations <10 μg/L are considered acceptable in occupational exposures (WHO 1980). In one estimate, workers with cumulative cadmium exposure equivalent to a blood concentration of 10 μg/L for 20 years would be expected to have a 14% incidence of renal dysfunction (Jarup et al. 1988).

Urine cadmium levels primarily reflect total body burden of cadmium, although urine levels do respond somewhat to recent exposure (Bernard and Lauwerys 1986). When the critical level for renal damage has been reached, urinary cadmium levels rise sharply because of the release of intrarenal cadmium along with decreased renal reabsorption of cadmium (see Section 2.3) (Lauwerys et al. 1994; Roels et al. 1981b). In the general population, the average urinary cadmium level is about 0.35 μg/g creatinine in nonsmokers and values above 2 μg/g creatinine are rare (Lauwerys and Malcolm 1985; Mueller et al. 1989). In populations with substantial environmental or occupational exposure, values can range up to 50 μg/g creatinine, even among individuals with no signs of renal dysfunction except high cadmium excretion levels (Falck et al. 1983; Roels et al. 1981b; Tohyama et al. 1988). In environmentally exposed individuals, Buchet et al. (1990) report that abnormal values of various biomarkers are found in 5% of the population with urinary excretion of cadmium above the 2-4 μg Cd/24 hour level (approximately l-3 μg/g creatinine). Based on a review of several cross-sectional epidemiological studies, Lauwerys et al. (1994) proposed a biological limit value of 5 nmol Cd/mmol creatinine (= 5 μg/g) and 2 nmol/mmol (≈ 2 μg/g) for adult male workers and the general population, respectively.

Fecal cadmium may be used as a direct indicator of daily dietary intake of cadmium because dietary cadmium is poorly absorbed in the gastrointestinal tract (see Section 2.3) (Kjellstrom et al. 1978). In workers exposed by inhalation, fecal cadmium has been used to estimate the amount of inhaled cadmium

transported to the gastrointestinal tract and the amount of dust ingested incidentally at work (Adamsson et al. 1979). Fecal cadmium primarily reflects recently ingested cadmium and, therefore, is not a good indicator of past cadmium exposure (Shaikh and Smith 1984).

Liver and kidney tissues preferentially accumulate cadmium, and concentrations of cadmium in liver and kidney may be measured *in vivo* by neutron activation analysis or in the kidney by X-ray fluorescence analysis (Christoffersson et al. 1987; Scott and Chettle 1986). Levels in both tissues increase with age and level of cadmium exposure, but kidney cadmium concentration tends to peak around age 50-60, while liver cadmium concentration continues to rise (see Section 2.3). Typical values for a 60-year-old North American with average environmental cadmium exposure are 25-40 μg/g wet weight in kidney cortex and l-3 μg/g wet weight in liver (Elinder 1985b). In workers exposed to cadmium by inhalation, values up to 300 μg/g wet weight in kidney and 100 μg/g wet weight in liver can be found (Christoffersson et al. 1987; Roels et al. 1981b). Because kidney cadmium content begins to decline after the onset of cadmium-induced renal dysfunction, liver cadmium may be a better indicator of cadmium exposure than kidney cadmium, and it has been suggested that kidney dysfunction is likely to appear at liver cadmium concentrations between 30 and 60 μg/g wet weight (Roels et al. 1981 b). *In vivo* liver and kidney cadmium measurements involving neutron activation analysis or X-ray fluorescence require complex and costly equipment and may pose a radiation hazard (Shaikh and Smith 1984), and those involving biopsy specimens (Lindqvist et al. 1989) require a painful and invasive procedure. Therefore, these methods for *in vivo* analysis are better suited for monitoring of occupationally exposed workers than environmentally exposed populations (Scott and Chettle 1986).

Hair levels of cadmium have been used as a measure of cadmium exposure, although the possibility of exogenous contamination has led to substantial controversy concerning the reliability of hair levels as a measure of absorbed dose (Frery et al. 1993; Hue1 et al. 1984; Lauwerys et al. 1994, Shaikh and Smith 1984; Wilhelm et al. 1990). Recent evidence has shown a correlation between cadmium levels in the hair of newborn infants and their mothers (Hue1 et al. 1984) and between cadmium levels in scalp and pubic hair (Wilhelm et al. 1990), indicating that among environmentally exposed populations, external contamination may not be significant for hair samples taken close to the scalp. Under occupational conditions, external contamination may be a more substantial problem (Shaikh and Smith 1984).

On the other hand, Frery et al. (1993) evaluated hair levels in a male population with a high expected exposure to tobacco smoke and in a population of pregnant woman and their newborns; they concluded that cadmium hair analysis was a reliable indicator for the subjects with the highest exposure, but was not sensitive enough to resolve differences for low level exposures, Newborn cadmium hair levels were a more

sensitive indicator than mother's hair, but the research was not able to determine if this was attributable to physiological changes or the lower reliability of the mother's head hair. Exogenous contamination is not considered a problem for newborn hair. The authors state that the variability introduced by exogenous contamination can be minimized by using the first 8 cm of hair from the scalp and by using careful washing techniques. There was also no significant difference between hair levels for passive or non-smokers indicating that either the above mentioned precautions worked or that the passive smoke source of exposure was not significant.

Cadmium measurements have been made on a variety of other biological materials, including milk (Schulte-Lobbert and Bohn 1977; Sikorski et al. 1989) placenta (Kuhnert et al. 1982; Roels et al. 1978; Saarenen et al. 1989), nails (Takagi et al. 1988), teeth (Sharon 1988), and cataractous lenses (Racz and Erdohelyi 1988). Although in some cases it could be established that levels in these tissues were higher among smokers than nonsmokers, the significance of cadmium levels as a marker of recent or total cadmium exposure has not been established for any of these tissues.

2.7.2 Biomarkers Used to Characterize Effects Caused by Cadmium

Acute inhalation exposure to high levels of cadmium causes respiratory damage and may lead to death. No information was located on biomarkers of respiratory effects in humans, but based on animal experiments, activity of alkaline phosphatase in the surfactant fraction of BALF has been suggested as a sensitive marker of pulmonary damage following acute cadmium inhalation (Boudrea et al. 1989). Such a biomarker of effect is not specific to cadmium exposure and would be most relevant to occupational exposures.

Renal dysfunction, usually first manifested as impaired tubular reabsorption of filtered solutes, is generally considered the primary toxic effect of chronic cadmium exposure (see Section 2.2). Impaired kidney function has been measured by increased levels of solutes (proteins, amino acids, uric acid, calcium, copper, phosphorous, etc.) in urine and/or serum. Excess urinary excretion of low-molecular-weight proteins and solutes is associated with decreased tubular reabsorption. Increased excretion of high molecular-weight proteins or decreased serum clearance of creatinine reflect glomerular dysfunction, which is generally associated with progressive renal damage (Roels et al. 1989). A brief discussion of the utility and limitations of several measures of tubular damage as biomarkers of effects of cadmium exposure is provided below.

Urinary β_2-microglobulin, a low molecular weight protein, has been widely used as an indicator of tubular renal dysfunction (Piscator 1984; Roels et al. 1981a; Smith et al. 1980). However, tubular renal dysfunction can be caused by exposures and diseases other than cadmium, so β_2-microglobulin is not a specific marker of cadmium-induced effects (Shaikh and Smith 1984). Practical considerations in using urinary β_2-microglobulin as a marker of tubular renal dysfunction include the need to control the pH of samples to prevent the rapid degradation that occurs at pH values below 5.5 (Shaikh and Smith 1984), and the fact that urinary β_2-microglobulin excretion normally rises with age (Roels et al. 1989).

Urinary retinol-binding protein is also considered to be a sensitive indicator of decreased tubular reabsorption, but it also is not specific for cadmium-induced damage in the kidney (Shaikh and Smith 1984; Topping et al. 1986). Retinol-binding protein is more stable in urine than β_2-microglobulin (Bernard and Lauwerys 1981) and appears to be of approximately equal sensitivity and specificity for detecting tubular proteinuria in cadmium-exposed populations (Topping et al. 1986). Levels of both proteins fluctuate over time, so regular, repeated sampling may be necessary to establish abnormal levels (Ormos et al. 1985).

Urinary metallothionein correlates with cadmium concentrations in liver, kidney, and urine (Shaikh and Smith 1984). Relatively strong correlations have been found between urinary metallothionein and urinary cadmium levels in exposed humans (Kawada et al. 1990), and a dose-related increase in urinary metallothionein was found in rats exposed to cadmium in drinking water for up to 2 years (Shaikh et al. 1989). However, the specificity of metallothionein for cadmium exposure may be questioned, because many other exposures are known to induce metallothionein (Waalkes and Goering 1990). Also, once renal damage becomes pronounced, urinary metallothionein levels increase sharply (Shaikh and Smith 1984).

Urinary N-acetyl-β-D-glucosaminidase (NAG), a lysosomal enzyme present in high concentrations in the proximal tubule, has a better correlation with urinary cadmium levels than does β_2-microglobulin at low cadmium exposure levels (urinary cadmium <10 ug/g creatinine) (Chia et al. 1989; Kawada et al. 1990; Mueller et al. 1989). However, increased urinary NAG activity can result from effects other than nephrotoxicity (Bernard and Lauwerys 1989).

Other enzymes, proteins, and amino acids in urine have been suggested as biological markers of incipient renal or liver damage resulting from cadmium exposure. Markers found to be sensitive indicators in exposed humans include β_2-microglobulin (Tohyama et al. 1986), trehalase (Iwata et al. 1988), alanine aminopeptidase (Mueller et al. 1989), and calcium (Buchet et al. 1990). Changes in urinary alkaline phosphatase, y-glutamyl transferase, urate, and phosphate tend to be significant only after other markers of

renal damage are clearly elevated (Mason et al. 1988). Several other enzymatic markers of cadmium induced renal damage have been suggested based on animal studies (Bomhard et al. 1984; Gatta et al. 1989; Girolami et al. 1989). Aminoaciduria has been found to be more sensitive than proteinuria for renal damage in animal studies (Nomiyama et al. 1975), but less sensitive in humans (Axelsson and Piscator 1966). At present, not enough information is available to determine which, if any, of these parameters provide sensitive and specific indicators of cadmium-induced renal damage.

At the present time, there is no single biological indicator for cadmium toxicity that is entirely adequate when considered alone. Measurement of cadmium levels in various biological materials can provide an indication of recent or total cadmium exposure, but the probability of adverse effects cannot be reliably predicted except at high exposure levels. Measurement of a variety of markers of renal dysfunction can provide a sensitive measure of early kidney toxicity, but cannot establish whether cadmium exposure was the cause.

There is also considerable controversy as to whether the critical concentration of urinary cadmium is closer to 5 μg Cd/g creatinine or to 10 μg Cd/g creatinine, corresponding to about 100 and 200 ppm in the kidney, respectively. Roels et al. (1993) correlated a number of markers with cadmium in blood and urine in a study population of workers occupationally exposed to cadmium from cadmium smelting operations. Three main groupings of thresholds were identified corresponding with different markers of effects: one around 2 μg Cd/g creatinine mainly associated with biochemical alterations (increased urinary 6-ketoprostaglandin F_{1x} and urinary sialic acid), a second around 4 μg Cd/g creatinine associated with increased excretion of high molecular weight proteins (possibly due to disruption of the glomerular membrane polyanionic charge) and tubular antigens or enzymes (BBA, NAG), and a third around 10 μg Cd/g creatinine associated with increased excretion of low molecular weight proteins and other indicators. The 10 μg Cd/g creatinine level had previously been proposed as the biological threshold for Cd-induced nephropathy. Whether the earlier changes are indicative of irreversible adverse renal effects remains an area of continued nvestigation.

To further evaluate the reversibility of proteinuria, Roels et al. (1997) studied the progression of Cd-induced renal tubular dysfunction in cadmium workers according to the severity of the microproteinuria at the time the exposure was substantially decreased. A total of 32 cadmium male workers was divided into two groups on the basis of historical records of urinary cadmium concentration (CdU) covering the period until 1984. The workers with CdU values of >10 μg Cd/g creatinine were subdivided further on the basis of the urinary concentration of β_2-microglobulin (β_2-MG-U) measured during the first observation period (1980-1984). In each group, the tubular microproteinuria as reflected by β_2-MG-U and the

concentration of retinol-binding protein in urine as well as the internal cadmium dose as reflected by the concentration of cadmium in blood and urine were compared between the first and second (1990-1992) observation periods. Increased microproteinuria was often diagnosed in cases with CdU values of >10 μg Cd/g creatinine. The progression of tubular renal function was found to depend on the extent of the body burden of cadmium (as reflected by CdU) and the severity of the initial microproteinuria at the time high cadmium exposure was reduced or ceased. When cadmium exposure was reduced and β_2-MG-U did not exceed the upper reference limit of 300 μg/g creatinine, the risk of developing tubular dysfunction at a later stage was likely to be low, even in cases with historical CdU values occasionally >10 but always <20 μg Cd/g creatinine. When the microproteinuria was mild β_2-MG-U >300 and < 1,500 μg/g creatinine) at the time exposure was reduced, and the historical CdU values had never exceeded 20 μg Cd/g creatinine, there was indication of a reversible tubulotoxic effect of cadmium. When severe microproteinuria (β_2MC-U >1,500 μg/g creatinine) was diagnosed in combination with historical CdU values exceeding 20 μg Cd/g creatinine, Cd-induced tubular dysfunction was progressive in spite of reduction or cessation of cadmium exposure.

For more information on biomarkers for renal and hepatic effects of chemicals see ATSDR/CDC *Subcommittee Report on Biological Indicators of Organ Damage* (1990). For information on biomarkers for neurological effects see OTA (1990).

2.8 INTERACTIONS WITH OTHER SUBSTANCES

Cadmium toxicity can be influenced by a wide variety of other chemicals. In humans, dietary deficiencies of calcium, protein, and vitamin D are likely to account for increased susceptibility to bone effects following cadmium exposure (Kjellstrom 1986). Iron deficiency has been shown to increase gastro-intestinal absorption of cadmium in humans (Flanagan et al. 1978), while oral zinc supplementation has been demonstrated to decrease the oral absorption of cadmium. No other information was located concerning interaction of cadmium with other chemicals in humans.

In animals, a few interactions following inhalation exposure have been evaluated. In rats exposed to cadmium chloride by inhalation, simultaneous exposure to zinc oxide prevents fatalities (Oldiges and Glaser 1986) and lung cancer (Oldiges et al. 1989). Exposure to an atmosphere containing 80% oxygen aggravated pulmonary damage from cadmium chloride inhalation in mice (Martin and Witschi 1985).

The toxicity of oral exposure to cadmium in animals has been shown to be influenced by several factors. In Japanese quail, cadmium toxicity was intensified by single or combined deficiencies of zinc, copper, iron,

calcium, and protein (Fox et al. 1979). A calcium-deficient diet in animals has been shown to aggravate cadmium immunotoxicity (Chopra et al. 1984) and fetotoxicity (Pond and Walker 1975). Simultaneous exposure to lindane increased the developmental toxicity of cadmium in rats (Saxena et al. 1986). Rats have an increased susceptibility to cadmium-induced bone loss due to multiple rounds of gestation and lactation (Bhattacharyya et al. 1988b) or ovariectomy (Bhattacharyya et al. 1988c), possibly related to associated effects on trace element status. Hopf et al. (1990) report that exposure to ethanol and cadmium in a liquid diet produced liver damage in rats at doses that were not separately hepatotoxic. In contrast, Kershaw et al. (1990) reported that ethanol pretreatment in male Sprague-Dawley rats substantially reduced the lethal and hepatotoxic properties of cadmium, possibly due to a reduced interaction between cadmium and target sites in liver organelles and cytosolic high-molecular-weight (HMW) proteins. Ethanol pretreatment in this study decreased (approximately 60%) the content of cadmium in nuclei, mitochondria, and endoplasmic reticulum, and nearly eliminated the association of cadmium with cytosolic HMW proteins. Reduction in the concentration of cadmium in potential target sites of intoxication was caused by a metallothionein-promoted sequestration of cadmium to the cytosol.

When cadmium is co-administered with ethanol in rats, there is a pronounced increase in cadmium accumulation in various regions of the brain (e.g., the corpus striatum and cerebral cortex). The cadmium is not bound to metallothionein, and there is a marked increase in lipid peroxidation and inhibition of membrane bound enzymes. Cadmium or ethanol alone did result in any effects on lipid peroxidation (Pal et al. 1993a, 1993b). Rats pretreated with acetaminophen are more sensitive to the renal toxicity of cadmium in water (Bernard et al. 1988a). Co-administration of lead and cadmium in the diet of rats had additive effects in reducing body weights, but neurologic toxicity was antagonized (Nation et al. 1990).

Numerous interactions have been demonstrated in animals using parenteral exposure, generally indicating that induction of metallothionein by pretreatment with zinc, selenium, or other metals, reduces toxicity of parenteral cadmium exposure (Gunn et al. 1968a, 1968b; Naruse and Hayashi 1989; Yamane et al. 1990). Zinc, calcium, or magnesium can prevent injection site, testicular, and prostatic cancers induced by subcutaneous or intramuscular injection of cadmium, but these interactions have been shown to be a complex phenomenon, dependent on dose, route, and target organ (Poirer et al. 1983; Waalkes et al. 1989). Mn(I1) pretreatment reduces Cd(II)-induced lethality (Goering and Klaassen 1985). Cadmium has been noted to have an inhibitory effect on manganese uptake (Gruden and Matausic 1989). In addition, manganese appears to be capable of increasing the synthesis of the metal-binding protein metallothionein. (Waalkes and Klaassen 1985). Data from a study by Goering and Klaasen (1985) suggest that manganese pretreatment increases the amount of Cd^{+2} bound to metallothionein, thereby decreasing hepatotoxicity due

to unbound Cd^{+2}. The significance of these observations to humans exposed to cadmium and manganese by the oral or inhalation routes is not clear.

Induction of hepatic metallothionein by cold stress reduced the acute toxicity of cadmium given by gavage to mice (Baer and Benson 1987). In addition to effects on metallothionein induction, substances may interact with cadmium by altering the competition among metal ions for enzyme or regulatory protein binding sites. For example, simultaneous administration of garlic (which is high in reduced sulfhydryl groups) decreases oral cadmium renal toxicity in rats (Cha 1987).

Coexposure to selenium reduced the clastogenic effect of cadmium on mouse bone marrow (Mukherjee et al. 1988b). Selenium deficiency enhances cadmium-induced cardiotoxicity possibly mediated via lipid peroxidation indicated by a significant reduction in the activities of the selenoenzyme, glutathione peroxidase. Selenium supplements in the diet prevented cadmium's cardiotoxic effect (Jamall and Smith 1985a). Selenium has also been shown to prevent testicular damage in rats (Kar et al. 1960; Omaye and Tappel 1975). In testes, selenium as selenite given before or during cadmium administration was shown to divert the binding of cadmium from low molecular proteins to higher molecular weight proteins (Chen et al. 1975; Whanger 1992). In contrast, Jamall and Smith (198%) report a shift in cadmium binding from metallothionein to lower weight proteins in kidney and liver from a diet supplemented with selenium compared to a selenium deficient diet. The selenium-cadmium interaction thus appears to be dependent on the duration and sequence of coexposure and possibly the organ-specific levels of selenoenzymes or other essential metals.

2.9 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to cadmium than will most persons exposed to the same level of cadmium 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 may result in reduced detoxification or excretion of cadmium, or compromised function of target organs affected by cadmium. Populations who are at greater risk due to their unusually high exposure to cadmium are discussed in Section 5.6, Populations With Potentially High Exposure.

Differences in individual sensitivity to cadmium have not been systematically studied, but based on what is known about cadmium toxicity, some inferences can be made. Populations with depleted stores of calcium, iron, or other dietary components due to multiple pregnancies and/or dietary deficiencies could be expected to have increased cadmium absorption from the gastrointestinal tract. Cadmium also is known to

dramatically increase resorption of bone calcium in animals fed calcium deficient diets, producing an Itai-Itai like syndrome. Animal studies have shown that young animals absorb more cadmium than adults (Sasser and Jarboe 1977, 1980) and that the bones of young animals are more susceptible to damage to cadmium than in older animals (Ogoshi et al. 1989). Infants and children may also have a higher rate of gastrointestinal absorption of cadmium, and their bones may be more susceptible to damage. Populations with kidney damage from causes unrelated to cadmium exposure, including diabetes, some drugs and chemicals, and the natural age-related decline in kidney function, could be expected to exhibit nephrotoxicity at lower cadmium exposures than those of normal healthy adults (Buchet et al. 1990).

Animal studies report conflicting results on the increased resistance or susceptibility of newborns and young for a variety of organ specific toxicities compared to adults, and the role of the relatively increased levels of metallothionein in the young on tissue distribution. There is some evidence to support the theory that high levels of metallothionein in young animals play an important role in their resistance to liver damage (Goering and Klaassen 1984), even though the increase in liver cadmium levels in the young compared to the adult (67% increase) is not as dramatic as the 10-fold increase in liver metallothionein. Wong and Klaassen (1980a) reported only a 30% increase in liver cadmium in 4-day-old rats and a 20-fold increase in liver metallothionein compared to the adults.

Further discussion of the susceptibility of children is found in Section 2.6, Children’s Susceptibility.

2.10 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to cadmium. 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 cadmium. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to cadmium:

Goldfrank LR, Flomenbaum NE, Lewin NA, et al. 1994. *Goldfrank’s Toxicologic Emergencies.* Fifth edition. Norwalk. CT: Appleton & Lange, 1063-1067.

Angle, CR. *Organ Specific Therapeutic Intervention.* 1995. Metal Toxicology Goyer RS, Klaassen CD, and Waalkes MP, eds. Academic Press, 78,82-83.

ATSDR. 1990. Agency for Toxic Substances and Disease Registry. Case *Studies in Environmental Medicine: Cadmiwn Toxicity,* Atlanta, GA.

2.10.1 Reducing Peak Absorption Following Exposure

Inhalation exposure to high concentrations of cadmium can be particularly dangerous because initial symptoms are often as mild as those associated with low-level exposure, and exposed individuals who are unaware either of the presence of cadmium or of the dangers of inhaling cadmium may allow exposure to continue until a harmful or even fatal dose is received (Beton et al. 1966; Lucas et al. 1980). Severe respiratory symptoms that may develop within a few hours of high-dose inhalation exposure include tracheobronchitis, pneumonitis, and pulmonary edema, accompanied by additional nonspecific flu-like symptoms (sweating, shivering, malaise) (Beton et al. 1966). Aside from removing a victim to fresh air and providing supportive medical care, no effective means have been reported for reducing absorption following inhalation exposure to cadmium (Bronstein and Currance 1988; EPA 1989d). Supportive medical care of individuals with inhalation exposure to high levels of cadmium includes monitoring for respiratory distress, assisting ventilation as needed, and administering humidified oxygen (Bronstein and Currance 1988; EPA 1989d). If pulmonary edema develops, individuals may be treated with supplemental oxygen, positive-pressure mechanical ventilation, administration of diuretics, intravenous fluids, and steroid medications. Antibiotic therapy and monitoring fluid balance (due to kidney function impairment) may also be required (Beton et al. 1966; Bronstein and Currance 1988; EPA 1989d; Haddad and Winchester 1990).

Oral exposure to cadmium is not an immediate threat because high doses are irritating enough to induce vomiting. In fact, the only known acute fatalities from oral exposure to cadmium followed intentional ingestion of high doses (Baker and Hafner 1961; Buckler et al. 1986; Frant and Kleeman 1941; Nordberg et al. 1973; Shipman 1986; Wisniewska-Knypl et al. 1971). Although inducing vomiting is sometimes recommended following ingestion of cadmium (Ellenhorn and Barceloux 1988; Stutz and Janusz 1988), concentrated cadmium solutions may be caustic, and esophageal damage could result from spontaneous or induced vomiting. Administration of water or milk may be indicated for patients able to swallow (Bronstein and Currance 1988; EPA 1989d). Administration of cathartics such as sorbitol or magnesium sulfate to enhance elimination from the gastrointestinal tract has been recommended (EPA 1989d; Stutz and Janusz 1988); however, the administration of activated charcoal to bind unabsorbed cadmium does not appear to be effective (ATSDR 1990; Ellenhorn and Barceloux 1988).

The intestinal absorption of cadmium at levels below those leading to gastrointestinal damage is relatively low (5-10% of the administered dose) (Flanagen et al. 1978; McLellan et al. 1978; Newton et al. 1984; Rahola et al. 1973). Other polyvalent cations including calcium, magnesium, and zinc can interfere with cadmium uptake (Foulkes 1985), but administration of competing cations can in some cases increase rather than decrease cadmium absorption (Jaeger 1990), and is, therefore, not recommended for the treatment of cadmium ingestion. Oral administration of some compounds that chelate cadmium such as meso-2,3-dimercaptosuccinic acid has been found in rodent studies to reduce absorption following acute oral exposure to cadmium, but other chelators such as dithiocarbamates can increase toxicity (see Section 2.3.1.2). At present, no recommendations for chelation treatment to reduce absorption can be made (Jones and Cherian 1990). Administration of garlic (which is high in reduced sulfhydryl groups) has been shown to decrease oral cadmium toxicity in rats (Cha 1987). Thus, use of garlic could be an area of future research.

Dermal or ocular exposure to high levels of cadmium may cause irritation (Wahlberg 1977) and should be treated by removing contaminated clothing, washing the skin, and thoroughly flushing the eyes (EPA 1989d; Stutz and Janusz 1988). These measures will also reduce the relatively small potential for dermal absorption of cadmium (see Section 2.3.1.3).

2.10.2 Reducing Body Burden

No effective means have been found to reduce the body burden of cadmium (ATSDR 1990; Goldfrank et al. 1994), although a variety of new chelating agents are actively being developed and tested (Cantilena and Klaassen 1981; Jones et al. 1992, 1994; Kostial et al. 1996; Singh and Jones 1995). Some of the more familiar chelators that are beneficial for other toxic metals actually increase cadmium toxicity by mobilizing the cadmium and substantially increasing the renal concentrations and toxicity (ATSDR 1990; Goldfrank et al. 1990; Jones and Cherian 1990). One such agent is the chelating agent dimercaprol (also known as BAL, British Anti-Lewisite), commonly used for treating cases of lewisite toxicosis. BAL is widely recognized as harmful in treating cadmium exposures. Some sources recommend using ethylenediamine tetraacetic acid (EDTA) salts (Ellenhorn and Barceloux 1988; Stutz and Janusz 1988) or use of EDTA with caution about potential nephrotoxicity (EPA 1989d; Haddad and Winchester 1990). Other promising chelators include diethylenetriaminepentaacetic acid (DTPA), 2,3-dimercaptosuccinic acid (DMSA), and various bis(carbodithioates).

Cantilena and Klaassen (1982) demonstrated the importance of rapid administration of DTPA, EDTA, or DMSA following acute cadmium exposure if they are to be effective. Waalkes et al. (1983) evaluated the role of metallothionein in the acute drop in chelator efficacy following cadmium poisoning in male Sprague- Dawley rats. Although the chelator, diethylenetriaminepentaacetic acid (DTPA), reduced cadmium content in the various organs when given immediately after cadmium, DTPA was ineffective at all later times. Increases in hepatic and renal metallothionein did not occur until 2 hours after cadmium, and did not coincide with the earlier drop in chelator efficacy. Blockade of metallothionein synthesis by actinomycin D treatment (1.25 mg/kg, 1 hour before Cd) failed to prolong the chelators effectiveness. Furthermore, newborn rats have high levels of hepatic metallothionein which had no effect on the time course of chelator effectiveness since DTPA still decreased cadmium organ contents, if given immediately following cadmium but had no effect if given 2 hours after cadmium. The authors concluded that metallothionein does not have an important role in the acute decrease in efficacy of chelation therapy for cadmium poisoning. The quick onset of chelator ineffectiveness may be due to the rapid uptake of cadmium into tissues, which makes it relatively unavailable of chelation.

Jones et al. (1992) reports on the development of a new series of monoalkyl esters of meso-2,3-dimercaptosuccinic acid, one of which, monoisoamyl meso-2,3-dimercaptosuccinate (Mi-ADMS), was an effective chelating agent for reduction of kidney and liver cadmium when administered either parenterally or orally. Jones et al. (1994) continue to evaluate monoaralkyl- and monoalkyl esters of DMS to develop chelators that can successfully remove “aged” cadmium deposits and that can be administered via a variety of routes. Eybl et al. (1994) demonstrated that Mi-ADMS, administered orally every 48 hours for 12 days after acute cadmium exposure, was effective at reducing cadmium in the kidney and liver, but not in the testes and brain.

Another area of chelation therapy research is in the use of multiple chelators. Blaha et al. (1995) evaluated the ability of two carbodithioate chelators, sodium N-(4-methylbenzyl)-4-O-(β-D-galactopyranosyl)-Dglucamine- N-carbodithioate (MeBLDTC) and sodium 4-carboxyamidopiperidine-N-carbothioate (INADTC), singly or in combination to reduce cadmium burden from chronically exposed rats. The combination therapy resulted in a synergistic effect on increased biliary excretion and reduced renal cadmium that, in the case of biliary excretion, was more than doubled that expected for a simple additive interaction.

Since cadmium is a cumulative toxin, individuals with known past high exposure to cadmium by either the oral or inhalation route should attempt to minimize further exposure (ATSDR 1990). Sources such as contaminated vegetable gardens and metal-working hobbies should be identified and controlled (ATSDR 1990). Cigarettes constitute a major source of cadmium exposure (Nordberg et al. 1983, and smokers would substantially reduce their further cadmium exposure by ceasing to smoke. Food is another major source of cadmium exposure (see Section 5.5). However, grains, cereal products, and potatoes, which are the major dietary sources of cadmium (Gartrell et al. 1986), are essential to a healthy diet. Therefore, no specific recommendations can be made at this time for a low-cadmium diet. Anemia enhances dietary cadmium absorption (Flanagen et al. 1978), so if anemia is present, successful treatment might reduce subsequent cadmium accumulation.

2.10.3 Interfering with the Mechanism of Action for Toxic Effects

The toxic effects of cadmium are generally thought to be caused by “free” cadmium ions; that is, cadmium not bound to metallothionein or other proteins (Goyer et al. 1989). However; cadmium bound to metallothionein may have the capacity to directly damage renal tubular membranes during uptake (Suzuki and Cherian 1987). Free cadmium ions may have a number of adverse effects, including inactivation of metal-dependent enzymes, activation of calmodulin, and initiation of the production of active oxygen species (Palmer et al. 1986; Waalkes and Goering 1990).

Respiratory damage caused by acute, high-level inhalation exposure to cadmium can cause impaired lung function that can last many years after exposure (Barnhart and Rosenstock 1984; Townshend 1982). No treatments other than supportive care and avoidance of additional risk factors for lung injury are presently known.

The kidneys appear to be the tissue most vulnerable to chronic cadmium exposure by either the oral or inhalation routes. The basis for the preferential sensitivity of the kidney is related to the filtering and reabsorption of circulating CdMT complex, which is then thought to be degraded in the tubular cell lysosomes and released as free intracellular cadmium. The toxic effect results from the limited ability of the kidney to synthesize new cytosolic metallothionein in response to an increasing cadmium load (Goyer et al. 1989). Cadmium bound to metallothionein, however, may also have nephrotoxic activity (Suzuki and Cherian 1987).

No treatments are currently available that specifically target free cadmium ions in the renal cortex, but zinc and calcium can stimulate metallothionein synthesis and may also compete with cadmium for enzyme binding sites (see Section 2.6). Thus, zinc, and/or calcium supplementation might help reduce renal cadmium toxicity, at least in zinc- or calcium-deficient individuals. It is not known whether administration of these compounds would be beneficial in individuals with adequate zinc and calcium intakes, and their clinical use is not currently recommended. Since one of the postulated mechanisms of cadmium toxicity is the stimulation and production of active oxygen species, it is possible that increasing the cellular levels of antioxidants such as superoxide dismutase, reduced sulfur compounds (particularly glutathione), vitamin C, vitamin E, or p-carotene could reduce renal cadmium toxicity by scavenging active oxygen species prior to reaction with cellular components. Adequate levels of selenium may also provide some protection against cadmium nephrotoxicity or cardiotoxicity. However, no data exist to indicate whether antioxidant treatment is actually beneficial in cases of cadmium toxicity, and antioxidants are not currently recommended for the treatment of cadmium-exposed humans.

Research in chelation therapy is promising for agents that can interfere or possibly reverse the toxic effec of cadmium. Xu et al. (1995, 1996) recently demonstrated that one of the more promising of DMSA derivatives, monoisoamyl meso-2,3-dimercaptosuccinate, when administered within 1 hour after acute exposure prevents the formation of cadmium-induced apoptotic DNA fragmentation and associated histopathological injury the testes of rats. Perry and Erlanger (1989) report a reversal of the cadmium induced hypertension in rats with the chelator d-myo-inositol-1,2,6-triphosphate.

Diabetes appears to make individuals more vulnerable to the renal effects of cadmium, and is itself a common causes of kidney damage (Buchet et al. 1990). Diabetics could reduce their risks of cadmium induced kidney toxicity by practicing good glycemic control and other measures to prevent diabetes-induced kidney damage. Cadmium exposure may increase calcium excretion and calcium loss from the bone especially in calcium deficient diets. This can be a substantial risk factor for pregnant women and for postmenopausal women who are prone to osteoporosis (Buchet et al. 1990). It might be prudent for women with elevated cadmium exposure to take steps to reduce their osteoporosis risk (e.g., hormone replacement therapy, dietary calcium and vitamin D supplementation, exercise). These measures, however, are based on limited data and should not be considered preventive of or therapeutic for cadmium toxicity until confirmed or refuted by future studies.

2.11 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 cadmium 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 cadmium.

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.

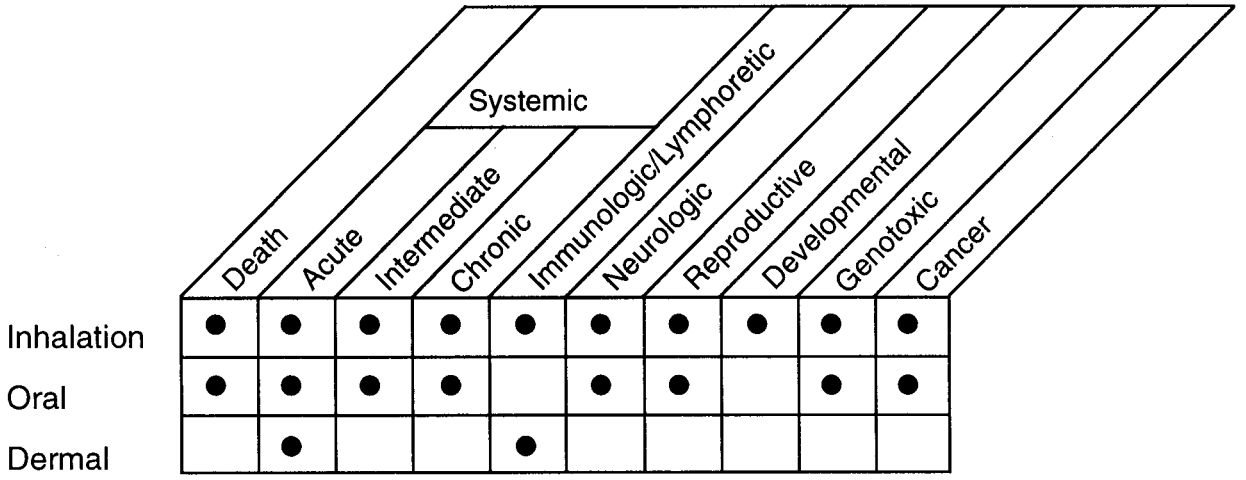
2.11.l Existing Information on Health Effects of Cadmium

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to cadmium are summarized in Figure 2-6. The purpose of this figure is to illustrate the existing information concerning the health effects of cadmium. 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.”

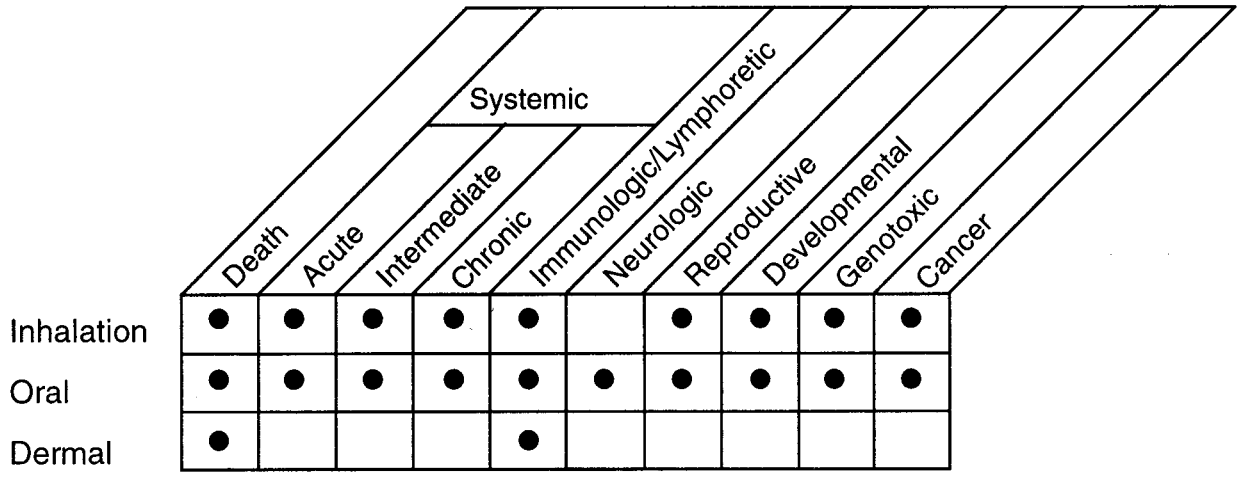
A data need, as defined in ATSDR’s *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

There is a massive database regarding the health effects of cadmium. In humans, the majority of studies have involved workers exposed by inhalation or residents of cadmium-polluted areas exposed primarily in the diet. Quantitative estimates of exposure levels are not available for many of these studies. Lethality, systemic toxicity, genotoxicity, and cancer have been studied in humans more extensively than

Figure 2-6. Existing Information on Health Effects of Cadmium



Human



Animal

● Existing Studies

immunotoxicity or neurotoxicity, with less being known about reproductive or developmental toxicity of cadmium in humans following inhalation or oral exposure. In animals, effects following oral exposures have generally been more thoroughly investigated than those following inhalation exposure, and few studies of cadmium toxicity following dermal exposure in humans were located.

2.11.2 Identification of Data Needs

Acute-Duration Exposure. Based on observations in both humans and animaIs, the target organ for inhalation exposure following acute exposure to cadmium is the lung; and the gastrointestinal tract is the target organ for oral exposure. Human respiratory or gastrointestinal toxicity has occurred after accidental exposures (Beton et al. 1966; Frant and Kleeman 1941; Lucas et al. 1980); Nordberg et al. 1973), but quantitative estimates of levels causing the effects are not reliable enough for comparison to animal data. Graham et al. (1978) reported the lowest no effect level for immunological effects from acute inhalation exposure to mice, but a human equivalent dose could not be derived to support an MRL. There is also no evidence for immunological effects in humans from acute inhalation exposure to cadmium. Additional information on immunological or other adverse effects and the associated no effect level from acute exposure to cadmium are needed to evaluate potential health effects and minimum risk levels in humans.

No reliable information was located regarding toxicity following dermal exposure to cadmium, but based on the lack of reported effects in the workers handling cadmium compounds, it seems unlikely that dermal exposure could deliver a significant dose of cadmium. It is apparent that acute toxicity occurs following inhalation or oral exposures at levels that are much higher than those likely to be received from environmental media, and establishing exposures at which respiratory or gastrointestinal effects occur in humans following acute exposure may not be essential for evaluating hazards to populations surrounding hazardous waste sites.

Intermediate-Duration Exposure. The kidney is likely to be the target organ following intermediate duration exposure to cadmium by the inhalation and oral routes, because of the preferential accumulation of cadmium in the kidney (Waalkes and Goering 1990). A variety of other systemic effects are known to occur following intermediate-duration cadmium exposure, particularly impaired lung function following inhalation exposure (Barnhart and Rosenstock 1984; Townshend 1982) and osteoporosis following oral exposure (Watanabe et al. 1986). However, the dose which led to these effects would most likely also lead

to kidney damage, even though some of the experiments did not allow sufficient follow-up time to demonstrate renal effects. Sufficient information from human or animal studies is not available to derive intermediate oral or inhalation MRLs, because estimates of levels of exposure for intermediate-durations causing renal effects in humans are not available. Investigation of long-term kidney toxicity expected from intermediate-duration exposure to cadmium is needed to evaluate risks to populations surrounding hazardous waste sites that may be exposed for limited periods. Studies of possible toxicity in animals following intermediate-duration dermal exposure to cadmium are needed to evaluate potential health effects in humans exposed to cadmium primarily by the dermal route.

Chronic-Duration Exposure and Cancer. The kidney is the main target organ following chronicduration exposure to cadmium by the inhalation and oral routes in both humans and animals. Loss of calcium from the bone and increased urinary excretion of calcium are associated with chronic cadmium exposure. The adverse effects on bone and calcium metabolism may be the result of a direct effect of cadmium or may be secondary to the renal damage and subsequent disruption of calcium metabolism and kinetics. Some studies indicate that disruption of calcium metabolism may be an earlier indicator of cadmium toxicity than the development of proteinuria. Additional studies are needed on the prevalence and mechanism of the cadmium-induced bone loss and wasting of calcium in humans.

Sufficient information from human studies is available to derive a chronic oral MRL (Nogawa et al. 1989). Additional investigation into the NOAEL in humans is needed to evaluate the minimum risk level from long-term inhalation exposure to cadmium. Better determinations of the critical concentration in the general population or in sensitive subpopulations and of the most sensitive indicator of kidney damage are also needed to evaluate risks of long-term cadmium exposure. No information was located regarding dermal toxicity of chronic cadmium exposure in humans or animals, and studies of dermal toxicity are needed to evaluate risks to populations exposed to cadmium primarily by dermal contact.

Evidence for the carcinogenicity of cadmium by the inhalation route is available from studies in rats (Takenaka et al. 1983). The evidence of carcinogenicity from human studies is limited, due to uncertainties in cadmium exposure estimates and confounding factors including exposure to arsenic, a known human lung carcinogen, and smoking (Kazantzis et al. 1992). Additional studies controlling for these exposures and providing more precise cadmium dose estimates are needed to provide more definitive evidence of the carcinogenic potential in humans of inhaled cadmium. Additional studies in animals are needed to evaluate the lack of an observed increase in lung cancer in mice and hamsters exposed to cadmium by inhalation

(Heinrich et al. 1989). Cadmium has not been shown to be carcinogenic following oral exposure in humans. In rats, however, cadmium increased tumors of the prostate, testes, and hematopoietic system (Waalkes et al. 1992). Additional lifetime-exposure studies in rats, mice, and hamsters orally exposed to cadmium at sufficiently high doses are needed to further define the carcinogenic potential of cadmium.

Zinc was reported to have an inhibitory effect on cadmium tumor formation in lungs and liver when mice are first dosed with the tumor promotor NDEA followed by a relatively high level of cadmium. Additional investigation of the zinc-related reduction of cadmium-induced tumors and zinc's effects on the mechanism of cadmium carcinogenesis is needed to evaluate the importance of the nutritional status of zinc in susceptible populations. Additional studies on the nutritional status and interactions of other essential metals (including selenium and copper) on cadmium carcinogenicity or cadmium's potential to induce a proliferative response are also needed.

Genotoxicity. The evidence for the genotoxicity of cadmium is mixed (see Tables 2-6 and 2-7). In vitro studies have provided both positive and negative results (Bruce and Heddle 1979; Oberly et al. 1982; Shirashi et al. 1972). Studies of chromosomdl aberrations in humans exposed to cadmium have also found both positive and negative results (Bui et al. 1975; Deknudt and Leonard 1975; O'Riordan et al. 1978; Tang et al. 1990). In animals, parenteral, but not oral, cadmium exposure has been found to cause germ cell mutations (Sutou et al. 1980; Watanabe and Endo 1982). Additional studies investigating effects in exposed humans using larger populations with quantitative estimates of exposure are needed to evaluate the human genotoxicity of cadmium.

Reproductive Toxicity. Only limited or conflicting evidence is available to evaluate the pptential for cadmium exposure to cause reproductive toxicity in humans. Some studies report no effect on male fertility (Gennart et al. 1992), male hormone levels (Mason 1990), sperm density (Noack-Fuller et al. 1992), or semen quality (Saaranen et al. 1989), while others report a reduction in sperm number or viability (Xu et al. 1993a). In one study, men occupationally exposed to cadmium at levels resulting in renal damage had no change in testicular function (Mason 1990). Adverse effects in animals from inhalation exposure have been reported including increased duration of the estrous cycle (Baranski and Sitarek 1987; Tsvetkova 1970), and increased relative testes weight but no loss in reproductive success (Kutzman et al. 1986). Adverse reproductive effects in animals from high-dose, acute, oral cadmium exposure have been reported including testicular atrophy and necrosis (Andersen et al. 1988; Bomhard et

al. 1987; Borzelleca et al. 1989) and decreased fertility (Kotsonis and Klaassen 1978; Machemer and Lorke 1981). At lower doses and intermediate exposures, adverse effects have included necrosis and atrophy of seminiferous tubule epithelium (Cha 1987); increased testes weight (Pleasants et al. 1992, 1993); increased prostatic hyperplasias (Waalkes and Rehm 1992); significantly increased relative testes weight, decreased sperm count and motility, decreased seminiferous tubular diameter, seminiferous tubular damage (Saxena et al. 1989); and decreased fertility (Sutou et al. 1980). Other animal studies for lower dose intermediate-exposures, however, report no adverse effects (Baranski et al. 1983; Bomhard et al. 1987; Groten et al. 1990; Kostial et al. 1993; Kotsonis and Klaassen 1978; Loeser and Lorke 1977a; Pleasants et al. 1992; Pond and Walker 1975; Zenick et al. 1982). Additional studies in animals, as well as retrospective, case-matched studies of reproductive success of populations for which occupational or environmental exposure to cadmium has been estimated, are needed to further evaluate the potential reproductive toxicity of cadmium in humans. Additional studies are needed (preferably with larger sample sizes) to evaluate the robustness of the association between cadmium and adverse effects on sperm.

Developmental Toxicity. The potential for cadmium exposure to cause developmental toxicity from pre- or postnatal exposures in humans is not known. One study in occupationally exposed women reported children with lowered birth weights, but with no increase in malformations (Tsetkova 1970). However, no control was made for parity, maternal weight, gestational age, or other factors known to influence birth weight. Many animal studies demonstrate that developmental toxicity may occur following cadmium exposure by oral routes with a relatively few studies reporting developmental effects following inhalation exposure (Ali et al. 1986; Baranski 1985, 1987; Baranski et al. 1983; Gupta et al. 1993; Machemer and Lorke 1981; Schroeder and Mitchener 1971; Webster 1978). Malformations of the skeleton effects, such as fused lower limbs, absence of one or more limbs, and delayed ossification of the sternum and ribs, have been reported. In addition, neurobehavioral end points such as locomotor activity and conditioned avoidance behavior were decreased. Retrospective, case-matched studies of developmental toxicity among children of women with known occupational or environmental exposure to cadmium are needed to evaluate the potential for cadmium exposure to cause human developmental toxicity such as skeletal malformations and neurobehavioral effects (as suggested in animal studies). Studies are also needed to follow-up on the results of increased susceptibility of young to bone damage (Ogoshi et al. 1989) or suppression of the immune response (Blakley 1985) reported in animals. The difference in the immune response (using the same protocol) between young mice (Blakley 1985) and older mice (Blakley 1988) should also be further evaluated. Studies of postnatal cadmium exposure to children, especially for children with diets deficient in calcium, protein, or iron, are needed to evaluate whether increased cadmium absorption from the diet leads to developmental effects.

Immunotoxicity. A variety of immunologic effects have been found in animals exposed to cadmium by the oral or inhalation routes (Blakley 1988; Bouley et al. 1984; Cifone et al. 1989a). However, the biological significance of these effects is not clear, and there is little information available on immunotoxicity in humans. Investigations of immunologic function of populations occupationally or environmentally exposed to cadmium, and follow-up mechanistic studies in animals are needed to evaluate the potential immunotoxicity of cadmium exposure in humans.

Neurotoxicity. A few studies have suggested an association between cadmium exposure in humans and impaired neuropsychologic functioning at levels below those causing nephrotoxicity (Hart et al. 1989b; Marlowe et al. 1985; Thatcher et al. 1982). Neurotoxicity has also been found in animal studies (Nation et al. 1984; Wong and Klaassen 1982). Additional studies to investigate neurologic effects in populations with known cadmium exposure, and studies of possible mechanisms of neurotoxicity in animals are needed to evaluate the potential neurotoxicity of cadmium exposure to humans. In addition, studies examining neurobehavioral end points in children would be useful.

Epidemiological and Human Dosimetry Studies. Cause/effect relationships for renal toxicity of cadmium have been derived from studies of workers occupationally exposed to cadmium by inhalation and of populations environmentally exposed to cadmium in the diet (Jarup et al. 198.5; Nogawa et al. 1989). Measurement of additional toxicity end points (musculoskeletal, reproductive, developmental, immunological, and neurological) in these well characterized populations are needed to evaluate whether any of these effects may occur at exposure levels below those leading to kidney damage. Additional development of physiologically based pharmacokinetic and pharmacodynamic models (PBPWPD models) is needed to evaluate human exposure scenarios.

Biomarkers of Exposure and Effect.

Exposure. Cadmium levels can be measured in a variety of tissues and fluids, including blood, urine, milk, liver, kidney, hair, and nails (Elinder and Lind 1985; Roels et al. 1981b; Sharma et al. 1982). Blood cadmium is a useful indicator of recent cadmium exposure, and urinary cadmium is a useful indicator of total body burden (Shaikh and Smith 1984). The most important indicator of the potential for toxicological injury is generally considered to be the cadmium concentration in the renal cortex, but individuals vary in the concentration causing renal effects (the “critical concentration”) (Roels et al. 1981b). Methods for in

vivo measurement of cadmium content in the kidney exist, but they are complex and expensive, and involve some exposure to ionizing radiation (Scott and Chettle 1986). Efforts to develop easier, safer, and less costly methods for *in vivo* analysis are needed, as well as studies to determine factors influencing individual variation in critical concentrations.

Effect. A number of sensitive tests are available to detect early stages of renal dysfunction that are known to be caused by cadmium exposure. These include analysis of urinary excretion of β_2-microglobulin, retinol-binding protein, or enzymes (Shaikh and Smith 1984). However, renal damage detected by these tests is not necessarily associated with cadmium exposure. Additional studies are needed to evaluate current or potentially new urinary or serum biomarkers in cadmium-exposed populations and their association with incipient injury to the kidney caused by cadmium.

Absorption, Distribution, Metabolism, and Excretion. Good information exists on cadmium toxicokinetics in humans and animals. PBPK/PD models have been developed to predict the critical organ dose as a function of route, duration, and level of exposure by the inhalation and oral routes (Kjellstrom and Nordberg 1978, 1985). Although general factors influencing absorption, distribution, metabolism, and excretion are known, additional studies are needed to provide information on metal metabolism and interactions that support quantitative evaluation of individual variations and resulting differences in renal cadmium accumulation. Very limited information exists on the dermal absorption of cadmium (Skog and Wahlberg 1964; Wester et al. 1992). Additional studies on the dermal absorption of cadmium are needed.

Comparative Toxicokinetics. Animal and human studies have generally reported comparable toxicokinetics of cadmium (Kjellstrom and Nordberg 1985; Nordberg 1985), suggesting that rats, mice, and rabbits are suitable models for cadmium toxicity in humans. However, some concerns have been raised about the appropriateness of the rat model for cadmium-induced lung tumors in humans because of differences in the morphology of the rat respiratory tract and resulting differences in cadmium particle deposition patterns and target cell populations. This is especially of concern because cadmium appears to be a contact carcinogen for lung cancer. Additional studies on the differences between the rat and human clearance rates, speciation at the level of the target cell, and protein transporters (as they relate to solubility and susceptibility) are needed to evaluate.the appropriateness of the rat model for predicting cadmium induced human lung cancers. Additional studies on differences in species, strain, sex, age, and other factors on cadmium kinetics and carcinogenic or other systemic effects are also needed to extrapolate the

animal data to potential human toxicity. Additional studies establishing the toxicokinetics of cadmium in pregnant animals are needed to assess the relevance of the developmental effects observed in animals.

Methods for Reducing Toxic Effects. The mechanisms of cadmium absorption across epithelial layers is likely to be via nonspecific mechanisms (Foulkes 1989). No methods are known for influencing absorption across the lung, but absorption across the gastrointestinal tract may be influenced by dietary status (Flanagan et al. 1978). Studies to determine whether dietary adjustments might help decrease cadmium uptake from food or water are needed. Studies to determine the effects of dietary deficiencies in calcium are needed to further evaluate the risk of cadmium exposure to susceptible populations. Uptake across the skin is probably sufficiently slow that simple washing of exposed areas is adequate to prevent excessive absorption (Skog and Wahlberg 1964).

Once cadmium is absorbed, it tends to accumulate in the kidney, which is the main target tissue for chronic low-dose exposure. The cellular and molecular basis for the preferential accumulation in the kidney is only partially understood (Waalkes and Goering 1990), and additional studies to define the rate-limiting steps in renal uptake and renal clearance of cadmium are needed to design strategies for reducing the rate of cadmium accumulation in this tissue. Additional studies on existing and new chelating agents and different treatment regimens are needed to improve the clinical therapies for acute and chronic exposures to cadmium.

The mechanism of cadmium toxicity in renal cells and other tissues probably involves binding of free cadmium ions to key cellular enzymes and proteins (Waalkes and Goering 1990). Thus, any agent that prevents cadmium from binding might help prevent toxicity. The endogenous cadmium-binding protein can serve this function; however, metallothionein-cadmium complexes may have renal toxicity (Suzuki and Cherian 1987). Additional studies on the role of metallothionein in cadmium toxicity are needed. Additional studies are needed on alternative substrate molecules or drugs that could interact with free cadmium and prevent binding to key cellular enzymes, as well as the ability of antioxidants to reduce damage from active-oxygen species produced by cadmium in tissues.

The impaired renal function that is the typical adverse effect of excessive cadmium exposure is neither clinically treatable nor reversible (ATSDR 1990; Roels et al. 1989). Studies on potential supportive treatment or remedies for cadmium-induced mild renal impairment would be valuable.

Children's Susceptibility. There is very little good information on the human health effects of cadmium, and virtually none for exposures to children. In part, this may be due to cadmium toxicity being primarily associated with either long-term low-level exposures, or to occupational inhalation. Moreover, critical toxic end points for children (developmental and neurological effects) have not been observed in human case histories even at doses that produce severe renal or musculoskeletal effects. Data needs relating to developmental effects are discussed in detail under the heading of developmental toxicity above. The data needs listed below address the health effects of cadmium for children from both acute and longer term exposures. Child health data needs relating to exposure are discussed in Section 5.8.1, Data Needs: Exposures of Children.

Additional research is needed on the toxicokinetics of cadmium during long-term low-level exposures *to* determine the potential long-term tissue burdens that are likely to result especially for the susceptible tissues of liver, kidney, and bone. Additional information is needed on cadmium transport across the blood-brain barrier in the developing fetus, and the role of metallothionein in the placenta.

Neurological and behavioral studies are needed that use the more sophisticated measures available today to evaluate children for *in utero,* acute, and longer term exposures. These studies should have the appropriate controls for confounding factors such as lead, parental use of ethanol, and Iiving conditions.

Additional studies are needed to evaluate whether or not biomarkers of cadmium exposure and effects that have been developed for adults are also applicable to children. If not, new biomarkers of exposure and effect need to be developed.

The effects of nutritional status (iron, zinc, and calcium levels) on cadmium absorption and accumulation in children need further evaluation. Improved regimens and choices for chelation therapy are also needed.

2.11.3 Ongoing Studies

A number of research projects are in progress investigating the health effects of cadmium. These projects are summarized in Table 2-8.

Table 2-8. Ongoing Studies on the Health Effects of Cadmium

Investigator	Affiliation	Research description	Sponsor
Tuan, RS	Thomas Jefferson University	Placental calcium-binding protein and calcium transport	NICHHD
Gairola, CG	University of Kentucky	Cigarette smoke--mechanisms of reproductive toxicity	NICHHD
Goldstein, SA	Yale University	Structure and function of the tok1 potassium channel	NIGMD
Hajdu, J	California State University Northridge	Structure and reactions of coordinated quinones	NIGMD
Williams, JC	University of Memphis	Microanalysis of physiological fluids and heart tissue	NIGMD
Penner-Hahn, JE	University of Michigan Ann Arbor	Structural character of metalloprotein metal site	NIGMD
Ellis, PD	Battelle Pacific Northwest Laboratories	Cadmium-113 nmr of systems of biological interest	NIGMD
Mason, AZ	California State University Long Beach	Processes of metal selection by metal accumulating cells	NIGMD
Weaver, A	Florida Agricultural and Mechanical Univ	Zinc dietary alterations of cadmium induced hepatic toxicity in rats	NIGMD
Latinwo, LM	Florida Agricultural And Mechanical Univ	Molecular basis of chromate and cadmium toxicity in mammalian systems	NIGMD
Marly, JI	Florida Agricultural And Mechanical Univ	Selenium compounds and cadmium induced toxicity in lung	NIGMD
Mrotek, JJ	Meharry Medical College	Characterizing cadmium effects at extracellular/intracellular adrenal cell sites	NIGMD
Gardea-Torresda, JL	University of Texas El Paso	Recovery of toxic heavy metals from contaminated water supplies using plants	NIGMD
Miller, DS	NIEHS	Intracellular receptors and metabolic control	NIEHS
Chapin, RE	NIEHS	Short-term comprehensive reproductive and developmental toxicity screen	NIEHS
Morgan, DL	NIEHS	Toxicity of chemicals used in the semiconductor industry	NIEHS
Helzlsouer, KJ	Johns Hopkins University	Molecular epidemiology of prostate cancer	NIEHS
Sens, DA	West Virginia University	Metallothionein isoforms and human nephrotoxicity	NIEHS
Hoorn, CM	Western Michigan University	Environmental toxicants and endothelial function	NIEHS
Bhattacharyya, MH	University of Chicago	Metallothionein in cadmium and radiation toxicity	NIEHS
Simpson, HJ	Mount Sinai School of Medicine	Urban heavy metal exposure--elemental and isotopic composition of samples	NIEHS
Callard, GV	Boston University	Neural and endocrine effects of environmental exposure to chemicals	NIEHS

Table 2-8. Ongoing Studies on the Health Effects of Cadmium (continued)

Investigator	Affiliation	Research description	Sponsor
Belitz, K	Dartmouth College	Subsurface transport and fate of cadmium, arsenic and lead	NIEHS
Friedland, AJ	Dartmouth College	Sources and mobility of lead and cadmium in soil, groundwater, and vegetation	NIEHS
Hamilton, JW	Dartmouth College	Molecular basis for effects of carcinogenic metals on inducible gene expression	NIEHS
Mirkes, PE	University of Washington	BCl 2, ROS, and cell death in developmental toxicity	NIEHS
Bieberich, CJ	American National Red Cross	Environmental toxicants effect on hox gene expression	NIEHS
Thiele, DJ	University of Michigan Ann Arbor	Metal detoxification in eukaryotic cells	NIEHS
Prozialeck, WC	Midwestern University	Mechanisms of cadmium toxicity in epithelial cells	NIEHS
Mills, John W	Clarkson University	Effect of heavy metals on the actin cytoskeleton	NIEHS
Mason, AZ	California State University Long Beach	Cadmium-induced alterations in copper metabolism	NIEHS
Welsh, MJ	University of Michigan at Ann Arbor	Mechanisms of toxicity in testes	NIEHS
Ruegg, CHE	University of Maryland Balt Prof School	Mechanisms underlying segment-specific nephrotoxicity	NIEHS
Liu, J	University of Kansas Medical Center	Protection against hepatotoxicity by oleanolic acid	NIEHS
Long, GJ	Olivet Nazarene University	Cadmium effects on calcium homeostasis and modulation	NIEHS
Lion, LC	Cornell University Ithaca	Enhanced pollutant desorption kinetics by bacterial extracellular polymers	NIEHS
Clements, WH	Colorado State University	The influence of previous exposure to a mixture of heavy metals on tolerance	NIEHS
Korrish, S	Harvard University	*In utero* PCB and metal exposure and infant development	NIEHS
Ford, TE	Harvard University	Assessment of metal contamination and ecological implications	NIEHS
Friedman, PA	Dartmouth College	Cellular cadmium transport in cultured kidney cells	NIEHS
Hinkle, PM	University of Rochester	Transport and actions of metal ions	NIEHS
Andrews, GK	University of Kansas Medical Center	Environmental toxicology using transgenic mouse models	NIEHS
Sunderman, FW, Jr	University of Connecticut Health Center	Zinc finger proteins as targets of metal embryotoxicity	NIEHS
Noelle, RJ	Dartmouth College	Mercury, cadmium, and B-lymphocyte function	NIEHS
Gandolfi, AJ	University of Arizona	Metal-metal interactions in the kidney	NIEHS
Fernando, Q	University of Arizona	Determination of toxic metal species with high energy ion beams	NIEHS

Table 2-8. Ongoing Studies on the Health Effects of Cadmium (continued)

Investigator	Affiliation	Research description	Sponsor
Conklin, MH	University of Arizona	Transport of trace metals in a polluted aquifer	NIEHS
Thomann, RV	New York University	Modeling transfer and bioaccumulation of metals in aquatic food webs	NIEHS
Ditoro, DM	New York University	Development of a sediment flux model for cadmium and chromium	NIEHS
Young, LY	New York University	Microbial mediated transformations of chromium and cadmium in the environment	NIEHS
Evans, HL	New York University	Behavioral and biochemical markers of neurotoxicity	NIEHS
Christie, NT	New York University	Assessment of oxidative DNA damage	NIEHS
Garte, S J	New York University	Molecular assays for toxicant exposure	NIEHS
Snyder, CA	New York University	Immune function assays as biomarkers of metal exposure	NIEHS
Costa, M	New York University	Methods to detect and predict exposure to toxic chemicals	NIEHS
Hammock, BD	University of California Davis	Immunochemical methods to monitor toxic substances in humans and other species	NIEHS
Hemond, HF	Massachusetts Institute of Technology	Chemical transport and human exposure on the aberjona watershed	NIEHS
Maines, MD	University of Rochester	Multiple forms of heme oxygenase--regulation by toxins	NIEHS
Petering, DH	University of Wisconsin Milwaukee	Cadmium, zinc, metallothionein and kidney toxicity	NIEHS
Ausiello, D	Mount Desert Island Biological Lab	Expression of atp channels in shark rectal gland in response to cadmium exposure	NIEHS
Kinne, R	Mount Desert Island Biological Lab	Effects of cadmium and mercury on Na-K-Cl cotransporter in shark rectal gland	NIEHS
Forrest, JN	Mount Desert Island Biological Lab	Cadmium, cobalt, nickel effect on signal transduction in shark rectal gland	NIEHS
Winge, DR	University of Utah	Metal chelation in proteins with polymetallic clusters	NIEHS
Shaikh, ZA	University of Rhode Island	Metallothionein and cadmium nephrotoxicity	NIEHS
Hart, BA	University of Vermont & State Agricultural College	Synthesis and role of metallothionein in the lung	NIEHS
Jones, MM	Vanderbilt University	Chelate antidotes for cadmium intoxication	NIEHS
Oberdoerster, G	University of Rochester	Mechanisms of particle and cadmium-induced lung injury	NIEHS
Klaassen, CD	University of Kansas Medical Center	Cadmium toxicology	NIEHS

Table 2-8. Ongoing Studies on the Health Effects of Cadmium (continued)

Investigator	Affiliation	Research description	Sponsor
Sauer, GR	University of South Carolina Columbia	Metal metabolism in calcifying cells	NIDR
Nation, JR	Texas A&M University Health Science Center	Heavy metals and cocaine--interactions	NIDR
Martin, Mary B	Georgetown University	Cadmium and breast cancer etiology	NCI
Ho, Shuk-Mei	Tufts University Medford	Metallothionein and cadmium carcinogenesis in rat prostate	NCI
Rubin, CS	Yeshiva University	Regulation and function of metallothionein genes	NCI
Walter, CA	University of Texas Health Sciences Center San Antonio	Carcinogenesis in metallothionein-deficient mice	NCI
Jacob, ST	Finch Univ of Health Sciences Chicago Med Sch	Role of metallothionein in cancer and drug resistance	NCI
Rossman, TG	New York University	Metallothionein--effects on mutagenesis	NCI
Lazo, JS	University of Pittsburgh Pittsburgh	Metallothioneins and electrophiles	NCI
Andrews, GK	University of Kansas Medical Center	Metallothionein in reproduction and development	NCI
Shuman, LM	University of Georgia	Equilibrium of metals in soils and effects on water quality	USDA
Parker, DR; Crowley, De	University of California Riverside	Potentially toxic metals as influenced by complexation in the rhizosphere	USDA
Kochian, LV	Agricultural Research Services Ithaca, NY	Phytoremediation of metal-polluted soils: mechanisms of heavy metal transport and accumulation	USDA
Grunes, DI; Norvell, WA	Agricultural Research Services Ithaca, NY	Factors limiting the availability to plants of essential and toxic elements in soils	USDA
Ow, DW	Agricultural Research Services Albany, CA	Defining the molecular cellular mechanisms of heavy metal chelation and sequestration in plants	USDA
Kochian, LV	Agricultural Research Services Ithaca, NY	Investigation of heavy metal bioaccumulation in plants grown on metal-polluted soils	USDA
Welch, RM; Norvell, WA; Grunes, DI	Agricultural Research Services Ithaca, NY	Uptake, transport and interaction of essential and toxic mineral elements in food crops	USDA
Kochian, LV; Norvell, WA; Grunes, DI	Agricultural Research Services Ithaca, NY	Cellular basis of essential and toxic mineral ion and absorption and translocation on food crops	USDA
Reeves, PG; Vanderpool, RA	Agricultural Research Services Grand Forks, ND	Health effects and bioavailability of cadmium from sunflower seed kernels: a human study	USDA

Table 2-8. Ongoing Studies on the Health Effects of Cadmium (continued)

Investigator	Affiliation	Research description	Sponsor
Chaney, RI; Wright, RJ	Agricultural Research Services Beltsville, MD	Soil and plant factors affecting concentration and bioavailability of cadmium in US. crops	USDA
Jones, RI	University of Illinois	Trace minerals in Illinois surface soils	USDA
Smith, DE	North Carolina State University	Effects of metal ions on *in vitro* estrogen action in rat uterus	USDA
Brams, EA	Prairie View A & M University	Toxic trace metals in an agricultural food chain: a quality assessment	USDA
Wagner, GJ	University of Kentucky	Characterization and modification of heavy metal accumulation in plants with emphasis on tobacco	USDA
Chang, AC; Page, AI; Amrhein, C	University of California Riverside	Chemistry and bioavailability of waste constituents in soils	USDA
Helmke, PA	University of Wisconsin	Ion exchange and complex ion formation affecting the solubility and plant uptake of trace elements	USDA
Blumenthal; SS	Department of Veteran Affairs - Medical Center Milwaukee, WI	Cadmium, zinc, metallothionein and kidney cytotoxicity	DVA-R&D
Bhattacharyya, MH	Argonne National Laboratory - Biological And Medical Research Division	Biochemical mechanisms of chemically induced health effects	DOE
Peterson, L	Francis Marion University	Synthesis and characterization of cadmium and zinc model compounds of biological relevance	NSF
Not specified	Grand Forks Human Nutrition Center	Health effects of cadmium from sunflower kernels: a human study	ILZRO
Not specified	McMaster University	Relationships of blood and urine cadmium levels to quantities of the element stored in the liver and kidney	ILZRO
Not specified	Universite Catholique de Louvain	Early biomarkers of health risks related to environmental exposure to toxic metals: validation in a prospective study	ILZRO
Lamm, SH	Consultants in Epidemiology and Occupational Health, Inc.	Further analysis of the globe, Colorado cohort for the relationship between lung cancer mortality rates and exposure to cadmium	Not specified

NICHHD = National Institute of Child Health And Human Development; NCI = National Cancer Institute; NIGMD = National Institute of General Medical Sciences; NIEHS = National Institute of Environmental Health Sciences; NIDR = National Institute of Dental Research; USDA = United States Department of Agriculture; DVA-R&D = Department of Veteran Affairs - Research and Development; DOE = US Department of Energy; NSF = National Science Foundation; ILZRO = International Lead Zinc Research Organization, Inc.

Source: FEDRIP 1998

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

Table 3-1 lists the common synonyms, trade names, and other pertinent identification information for cadmium and its most important compounds

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Table 3-2 lists important physical and chemical properties of cadmium and its most important compounds.

Table 3-1. Chemical Identity of Cadmium and Compounds[a]

Characteristic	Cadmium	Cadmium carbonate	Cadmium chloride
Synonym(s)	Colloidal cadmium	Otavite [b]; cadmium monocarbonate; carbonic acid; cadmium salt	Caddy [b]; Vi-Cad [b]; cadmium dichloride; dichlorocadmium
Registered trade name(s)	No data	No data	No data
Chemical formula	Cd [b]	$CdCO_3$ [b]	$CdCl_2$ [b]
Chemical structure	Cd [b]	$CdCO_3$ [b]	$CdCl_2$ [b]
Identification numbers:			
CAS registry	7440–43–9 [b]	513–78–0 [b]	10108–64–2
NIOSH RTECS	EU9800000	FF9320000	EV0175000
EPA hazardous waste	D006	D006	D006
OHM/TADS	7216622	No data	7217229
DOT/UN/NA/IMCO shipping	UN2570/IMCO 6.1	UN2570/IMCO 6.1	NA2570/IMCO 6.1
HSDB	282	1612	278
NCI	No data	No data	No data

Characteristic	Cadmium oxide	Cadmium sulfate	Cadmium sulfide
Synonym(s)	Cadmium fume; cadmium monoxide	Cadmium sulphate; Sulfuric acid; cadmium (2+) salt	Cadmium monosulfide; Cadmium yellow; Cadmium orange; Cadmopur yellow; Greenockite[b]; Capsebon [b]
Registered trade name(s)	No data	No data	No data
Chemical formula	CdO [b]	$CdSO_4$ [b]	CdS [b]
Chemical structure	CdO [b]	$CdSO_4$ [b]	CdS [b]
Identification numbers:			
CAS registry	1306–19–0 [b]	10124–36–4 [b]	1306–23–6 [b]
NIOSH RTECS	EV1925000	EV2700000	EV3180000
EPA hazardous waste	D006	D006	D006
OHM/TADS	No data	7217231	No data
DOT/UN/NA/IMCO shipping	UN2570/IMCO 6.1	UN2570/IMCO 6.1	NA2570/IMCO 6.1
HSDB	1613	274	1614
NCI	CO2551	No data	CO2711

[a]All information obtained from HSDB 1996 except where noted
[b]Merck 1989

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 3-2. Physical and Chemical Properties of Cadmium and Compounds[a]

Property	Cadmium	Cadmium carbonate	Cadmium chloride
Molecular weight	112.41 [b]	172.42 [b]	183.32
Valence	2 [b]	2	2
Color	Silver-white [b]	White [c]	Colorless
Physical state	Lustrous solid	Powder or rhombohedral leaflets [b]	Rhombohedral crystals [b]
Melting point	321 °C [b]	Decomposes at <500 °C [g]	568 °C [b]
Boiling point	765 °C [b]	No data	960 °C [b]
Density	8.65 g/cm^3 at 25 °C [b]	4.26 g/cm^3 at 4 °C [g]	3.33 g/cm^3 at 20 °C [b]
Odor	Odorless	No data	Odorless[c]
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water	Insoluble [b]	Insoluble [g]	Soluble [b]
Organic solvent(s)	Acids, NH_4NO_3, hot H_2SO_4 [g]	Dilute acid, concentrated NH_4 solution[c]	Acetone, slightly soluble in MEOH and ETOH [b]
Partition coefficients:			
Log K_{ow}	No data	No data	No data
Log K_{oc}	No data	No data	No data
Vapor pressure	1 mmHg at 394 °C [e]	No data	10 mm Hg at 656 °C [e]; 40 mm Hg at 736 °C [d]; 760 mm Hg at 967 °C [d]
Henry's law constant	No data	No data	No data
Autoignition temperature	250 °C	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	No data	No data	No data
Conversion factors:	No data	No data	No data
Explosive limits	No data	No data	No data

Table 3-2. Physical and Chemical Properties of Cadmium and Compounds (continued)

Property	Cadmium oxide	Cadmium sulfate	Cadmium sulfide
Molecular weight	128.41 [b]	208.47 [b]	144.47 [b]
Valence	2	2	2
Color	Dark brown [b]	Colorless [c]	Light yellow or orange [b]
Physical state	Infusible powder or cubic crystals [b]	Monoclinic crystals [b]	Cubic or hexagonal crystals [b]
Melting point	No data	1,000 °C [g]	1,750 °C [g]
Boiling point	Sublimes at 1,559 °C [c]	No data	Sublimes in N_2 at 980 °C [c]
Density	Crystals 8.15 g/cm^2 ; amorphous powder 6.95 g/cm^3 [c]	4.69 g/cm^3 [b]	4.82 g/cm^3, hexagonal structure [b]; 4.5 g/cm^3, cubic structure [b]
Odor	Odorless	Odorless [b]	No data
Odor threshold:			
Air	No data	No data	No data
Water	No data	No data	No data
Solubility:			
Water	Insoluble [b]	Soluble [c]	Soluble at 1.3 mg/L at 18 °C [b]
Organic solvent(s)	Dilute acids, slowly soluble in NH4 salts [b]	Insoluble in alcohol, acetone, ammonia [g]	Concentrated or warm dilute mineral acids [b]
Partition coefficients:			
Log K_{ow}	No data	No data	No data
Log K_{oc}	No data	No data	No data
Vapor pressure	1 mm Hg at 1,000 °C [e]	No data	No data
Henry's law constant	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	No data	No data	No data
Conversion factors	No data	No data	No data
Explosive limits	No data	No data	No data

[a] All information obtained from HSDB 1996 unless otherwise noted
[b] Merck 1989
[c] Lewis 1993
[d] Farnsworth 1980
[e] Sax and Lewis 1989
[f] Clayton and Clayton 1981
[g] Weast 1994

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

4.1 PRODUCTION

Cadmium is a widely but sparsely distributed element found in the earth's crust at concentrations ranging from 0.1 to 1 ppm, primarily in association with zinc ores (Elinder 1985a; IARC 1993). Approximately 3 kilograms of cadmium for each ton of zinc are produced (OECD 1994). As a by-product of zinc processing, cadmium production has closely followed the demand for zinc. Between 1993 and 1997, the annual cadmium production in the United States rose from 1,090 to 2,060 metric tons (USGS 1999). A strong demand for cadmium worldwide, particularly in the nickel-cadmium battery industry, contributed to increases in domestic cadmium production in the 1980s followed by lower production levels in the early 1990s (Llewellyn 1988; OECD 1994).

Two companies were listed as producing all of the primary cadmium in the United States during 1997: Big River Zinc Corporation (Korea Zinc Co., Ltd), Saugett, Illinois; and Savage Zinc Inc., Clarksville, Tennessee (Llewellyn 1988; USGS 1997). Approximately 20% of the ores processed in Illinois are imported; the Savage Zinc operation processes Tennessee and Kentucky ores. A third company in Pennsylvania, International Metals Reclamation Co. Inc., recovers cadmium from spent nickel-cadmium batteries (Ni-Cd) (USGS 1997); this company began reclaiming cadmium in 1995 and processes about 3,500 tons of spent Ni-Cd batteries annually. It is projected that 50% of Ni-Cd batteries will be recycled by 2002 (USGS 1997).

The following companies are currently cited as major producers of other cadmium compounds: Big River Zinc Corporation, Saugett, Illinois (cadmium oxide); Shepherd Chemical Company, Cincinnati, Ohio (cadmium carbonate); Engelhard Corporation, Cleveland, Ohio (cadmium chloride, cadmium sulfate, and cadmium sulfide/sulfoselenide pigments); and Eagle-Picher Industries, Inc., Milwaukee, Wisconsin (cadmium sulfide-orange cadmium) (SRI 1994). Companies specifically cited as major producers of cadmium sulfide/sulfoselenide pigments include Morton Internationals, Inc., Danvers, Massachusetts; Cerac Incorporated, Milwaukee, Wisconsin; SCM Chemicals, Inc., Baltimore, Maryland; and Warner-Jenkinson Cosmetic Colors, South Plainfield, New Jersey (SRI 1994).

Table 4-l lists the facilities in each state that manufacture or process cadmium, the intended use, and the range of maximum amounts of cadmium that are stored on site. The data listed in Table 4-1 are derived from the Toxics Release Inventory (TRI) (TRI961998). Because only certain types of facilities were required to report, this is not an exhaustive list.

Cadmium metal is available in purities ranging from 99.9 to 99.9999% in the following grades: technical, powder, pure sticks, ingots, slabs, high-purity crystals (<10 ppm impurities), and a form called mossy that is used in electroplating (NTP 1991). Cadmium (as cadmium oxide) is obtained mainly as a byproduct during the processing of zinc-bearing ores (e.g., sphalerites), and also from the refining of lead and copper from sulfide ores (e.g., galena and malachite) (HSDB 1990; IARC 1993; Muntau and Baudo 1992; U.S. Bureau of Mines 1990). Cadmium oxide produced during roasting of ores is reduced with coke, and cadmium metal is separated by distillation or electrodeposition (Elinder 1985a). Commercial-grade cadmium oxide is available in the United States with a purity of 99.7%; common impurities are lead and thallium (NTP 1991). Cadmium chloride is produced by reacting molten cadmium with chlorine gas at 600 ^{o}C or by dissolving cadmium metal or the oxide, carbonate, sulfide, or hydroxide in hydrochloric acid and subsequently vaporizing the solution to produce a hydrated crystal (HSDB 1994; IARC 1993). In preparing the anhydrous cadmium chloride salt, the hydrate is refluxed with thionyl chloride or calcined in a hydrogen chloride atmosphere (HSDB 1994; IARC 1993). The commercial grade available in the United States typically contains about 51% cadmium and 0.005% each of iron and copper; high purity grades (99.9%) are also available (NTP 1991).

The commercial preparation of cadmium sulfate usually involves dissolution of the metal oxide, carbonate, or sulfide in sulfuric acid with subsequent cooling or evaporation (HSDB 1994). Anhydrous cadmium sulfate is prepared by oxidation of the sulfide or sulfite at elevated temperatures; by the action of dimethyl sulfate on finely powdered cadmium nitrate, halides, oxide, or carbonate; or by melting cadmium with ammonium or sodium peroxodisulfate (IARC 1993). Cadmium sulfate monohydrate, which is the cadmium compound most often marketed, is produced by evaporating a cadmium sulfate solution above 41.5 ^{o}C (IARC 1993). Cadmium sulfate is available in technical and C.P. (chemically pure) grades (NTP 1991). Cadmium sulfide can be prepared by reacting hydrogen sulfide with cadmium vapor at 800 ^{o}C, or by heating a mixture of cadmium or cadmium oxide with sulfur (IARC 1993). Cadmium sulfide is available in technical, N.D., high-purity (single crystals), and commercial grades (NTP 1991). Cadmium carbonate is produced by absorption of carbon dioxide in a cadmium hydroxide solution (HSDB 1994).

Table 4-1. Facilities That Manufacture or Process Cadmium

FACILITY	LOCATION[a]	RANGE OF MAXIMUM AMOUNTS ON SITE IN POUNDS	ACTIVITIES AND USES
BIRMINGHAM STEEL CORP.	BIRMINGHAM , AL	100 - 999	ARTICLE COMPONENT
HALL CHEMICAL CO.	ARAB , AL	10,000 - 99,999	PRODUCE , IMPORT , SALE/DISTRIBUTION , REACTANT
MONSANTO CO.	DECATUR , AL	10,000 - 99,999	CHEMICAL PROCESSING AID,PRODUCE , BYPRODUCT
SANDERS LEAD CO. INC.	TROY , AL	10,000 - 99,999	PRODUCE , BYPRODUCT , IMPURITY
TUSCALOOSA STEEL CORP.	TUSCALOOSA , AL	1,000 - 9,999	ARTICLE COMPONENT
GNB TECHS. INC.	FORT SMITH , AR	1,000 - 9,999	ARTICLE COMPONENT
NUCOR-YAMATO STEEL CO.	BLYTHEVILLE , AR	0 - 99	PRODUCE , BYPRODUCT
ASARCO INC.	HAYDEN , AZ	50,000,000 - 99,999,999	PRODUCE , IMPORT , ON-SITE USE/PROCESSING , SALE/DISTRIBUTION , BYPRODUCT IMPURITY , REACTANT
BHP COPPER METALS CO.	SAN MANUEL , AZ	1,000 - 9,999	PRODUCE , BYPRODUCT , IMPURITY
CYPRUS MIAMI MINING CORP.	CLAYPOOL , AZ	100 - 999	PRODUCE , IMPURITY
ALERT PLATING CO.	SUN VALLEY , CA	1,000 - 9,999	ARTICLE COMPONENT
BURBANK PLATING SERVICES CORP.	PACOIMA , CA	100 - 999	PRODUCE , ON-SITE USE/PROCESSING , ARTICLE COMPONENT , MANUFACTURING AID , ANCILLARY/OTHER USE
EME INC.	COMPTON , CA	100 - 999	CHEMICAL PROCESSING AID
EAGLE-PICHER IND. INC.	COLORADO SPRINGS , CO	10,000 - 99,999	REACTANT
ANSONIA COPPER & BRASS INC.	ANSONIA , CT	10,000 - 99,999	ARTICLE COMPONENT
FLOW POLYMERS INC.	STRATFORD , CT	10,000 - 99,999	IMPORT , ON-SITE USE/PROCESSING , FORMULATION COMPONENT , REPACKAGING
HANDY & HARMAN	FAIRFIELD , CT	10,000 - 99,999	ARTICLE COMPONENT
SYNTHETIC PRODS. CO.	STRATFORD , CT	100,000 - 999,999	PRODUCE , ON-SITE USE/PROCESSING , REACTANT , FORMULATION COMPONENT
EVEREADY BATTERY CO. INC.	ALACHUA , FL	100,000 - 999,999	PRODUCE , ON-SITE USE/PROCESSING , REACTANT , ARTICLE COMPONENT
JEFFERSON SMURFIT CORP.	JACKSONVILLE , FL	10,000 - 99,999	ANCILLARY/OTHER USE
ARMSTRONG GLASS CO. INC.	ATLANTA , GA	100 - 999	FORMULATION COMPONENT
SAFT AMERICA INC.	VALDOSTA , GA	100,000 - 999,999	PRODUCE , ON-SITE USE/PROCESSING , REACTANT , ARTICLE COMPONENT
TECHNICAL COATINGS CORP.	ALPHARETTA , GA	0 - 99	FORMULATION COMPONENT
BLOOMFIELD FNDY. INC.	BLOOMFIELD , IA	0 - 99	PRODUCE , IMPURITY
FMC CORP.	POCATELLO , ID	1,000,000 - 9,999,999	PRODUCE , BYPRODUCT
API IND. INC.	ELK GROVE VILLAGE , IL	10,000 - 99,999	PRODUCE , ON-SITE USE/PROCESSING , BYPRODUCT , ARTICLE COMPONENT , CHEMICAL PROCESSING AID
BIG RIVER ZINC CORP.	SAUGET , IL	100,000 - 999,999	PRODUCE , SALE/DISTRIBUTION , BYPRODUCT
CALUMET STEEL CO.	CHICAGO HEIGHTS , IL	10,000 - 99,999	FORMULATION COMPONENT
CHEMETCO INC.	HARTFORD , IL	100,000 - 999,999	PRODUCE , IMPORT , IMPURITY
GNB TECHS. INC.	KANKAKEE , IL	10,000 - 99,999	ARTICLE COMPONENT
THREE J'S IND. INC.	ELK GROVE VILLAGE , IL	1,000 - 9,999	PRODUCE , ON-SITE USE/PROCESSING , BYPRODUCT , CHEMICAL PROCESSING AID
GE PLASTICS CO.	MOUNT VERNON , IN	10,000 - 99,999	FORMULATION COMPONENT , ANCILLARY/OTHER USE
JUPITER ALUMINUM CORP.	HAMMOND , IN	1,000 - 9,999	ARTICLE COMPONENT
UNITED TECHS. AUTOMOTIVE INC.	EDINBURGH , IN	10,000 - 99,999	ARTICLE COMPONENT
ESSEX GROUP INC.	HOISINGTON , KS	10,000 - 99,999	ARTICLE COMPONENT
CONDEA VISTA CO.	JEFFERSONTOWN , KY	100,000 - 999,999	FORMULATION COMPONENT
ENGELHARD CORP.	LOUISVILLE , KY	10,000 - 99,999	PRODUCE , ON-SITE USE/PROCESSING , SALE/DISTRIBUTION , REACTANT
NEWPORT STEEL CORP.	WILDER , KY	10,000 - 99,999	ARTICLE COMPONENT
LIBBEY GLASS INC.	SHREVEPORT , LA	10,000 - 99,999	ARTICLE COMPONENT
NAN YA PLASTICS CORP. AMERICA	BATCHELOR , LA	100,000 - 999,999	FORMULATION COMPONENT
ATTLEBORO REFINING CO. INC.	ATTLEBORO , MA	0 - 99	ANCILLARY/OTHER USE

Table 4-1. Facilities That Manufacture or Process Cadmium (continued)

FACILITY	LOCATION[a]	RANGE OF MAXIMUM AMOUNTS ON SITE IN POUNDS	ACTIVITIES AND USES
CHEMET CORP.	ATTLEBORO , MA	1,000 - 9,999	ARTICLE COMPONENT
SCM GLIDCO ORGANICS CORP.	BALTIMORE , MD	100,000 - 999,999	PRODUCE , IMPORT , ON-SITE USE/PROCESSING , SALE/DISTRIBUTION , REACTANT
AJAX METAL PROCESSING INC.	DETROIT , MI	1,000 - 9,999	CHEMICAL PROCESSING AID
DIECAST CORP.	JACKSON , MI	10,000 - 99,999	ARTICLE COMPONENT
ELM PLATING CO.	JACKSON , MI	0 - 99	ARTICLE COMPONENT
ROUGE STEEL CO.	DEARBORN , MI	1,000 - 9,999	FORMULATION COMPONENT
ASARCO INC.	ANNAPOLIS , MO	1,000 - 9,999	PRODUCE , ON-SITE USE/PROCESSING , SALE/DISTRIBUTION , BYPRODUCT , REACTANT
DOE RUN CO.	HERCULANEUM , MO	100,000 - 999,999	PRODUCE , IMPURITY
M. A. HANNA COLOR	SAINT PETERS , MO	1,000 - 9,999	FORMULATION COMPONENT
IPC CORINTH DIV. INC.	CORINTH , MS	1,000 - 9,999	ARTICLE COMPONENT
NORTH AMERICAN PLASTICS INC.	PRAIRIE , MS	100 - 999	FORMULATION COMPONENT
ASARCO INC.	EAST HELENA , MT	1,000,000 - 9,999,999	PRODUCE , IMPORT , ON-SITE USE/PROCESSING , SALE/DISTRIBUTION , BYPRODUCT IMPURITY , REACTANT
KOBE COPPER PRODS. INC.	PINE HALL , NC	1,000,000 - 9,999,999	REPACKAGING , ANCILLARY/OTHER USE
AMERICAN MICROTRACE CORP.	FAIRBURY , NE	10,000 - 99,999	PRODUCE , BYPRODUCT
LUCENT TECHS. INC.	OMAHA , NE	10,000 - 99,999	ARTICLE COMPONENT
YANKEE HILL BRICK MFG. CO.	LINCOLN , NE	1,000 - 9,999	IMPORT , BYPRODUCT
AKCROS CHEMICALS AMERICA	NEW BRUNSWICK , NJ	10,000 - 99,999	PRODUCE , IMPORT , ON-SITE USE/PROCESSING , SALE/DISTRIBUTION , REACTANT FORMULATION COMPONENT
DEGUSSA CORP.	SOUTH PLAINFIELD , NJ	1,000 - 9,999	SALE/DISTRIBUTION , FORMULATION COMPONENT , ARTICLE COMPONENT
DURAND GLASS MFG. CO.	MILLVILLE , NJ	100 - 999	IMPORT , ON-SITE USE/PROCESSING , ARTICLE COMPONENT
GENTEK BUILDING PRODS.	WOODBRIDGE , NJ	100 - 999	ARTICLE COMPONENT
M.C. CANFIELD INC.	UNION , NJ	100 - 999	FORMULATION COMPONENT
METAL IND. CORP.	RIVERSIDE , NJ	100 - 999	PRODUCE , SALE/DISTRIBUTION , FORMULATION COMPONENT , REPACKAGING
CHINO MINES CO.	HURLEY , NM	100,000 - 999,999	PRODUCE , BYPRODUCT , IMPURITY
AMPHENOL CORP.	SIDNEY , NY	1,000 - 9,999	ARTICLE COMPONENT
BELMONT METALS INC.	BROOKLYN , NY	10,000 - 99,999	ARTICLE COMPONENT
H. M. QUACKENBUSH INC.	HERKIMER , NY	1,000 - 9,999	ARTICLE COMPONENT
NEY SMELTING & REFINING CO.	BROOKLYN , NY	1,000 - 9,999	FORMULATION COMPONENT , ARTICLE COMPONENT , REPACKAGING
THOMAS & BETTS	HORSEHEADS , NY	1,000 - 9,999	ARTICLE COMPONENT
AK STEEL CORP.	MIDDLETOWN , OH	1,000 - 9,999	ANCILLARY/OTHER USE
BARKER PRODS.	CLEVELAND , OH	1,000 - 9,999	IMPORT , REACTANT
DOVER CHEMICAL CORP.	DOVER , OH	10,000 - 99,999	IMPORT , ON-SITE USE/PROCESSING , FORMULATION COMPONENT
ERIEVIEW METAL TREATING CO.	CLEVELAND , OH	1,000 - 9,999	ARTICLE COMPONENT
FERRO CORP.	CLEVELAND , OH	100,000 - 999,999	PRODUCE , ON-SITE USE/PROCESSING , SALE/DISTRIBUTION , REACTANT , FORMULATION COMPONENT
FERRO CORP.	WALTON HILLS , OH	100,000 - 999,999	PRODUCE , ON-SITE USE/PROCESSING , SALE/DISTRIBUTION , REACTANT , FORMULATION COMPONENT
GENERAL COLOR & CHEMICAL CO.	MINERVA , OH	10,000 - 99,999	FORMULATION COMPONENT , REPACKAGING
HOHMAN PLATING & MFG. INC.	DAYTON , OH	10,000 - 99,999	ARTICLE COMPONENT
LIBBEY GLASS INC.	TOLEDO , OH	100,000 - 999,999	ARTICLE COMPONENT
N & W METAL FINISHING INC.	CLEVELAND , OH	1,000 - 9,999	ARTICLE COMPONENT
NORTH STAR STEEL	YOUNGSTOWN , OH	10,000 - 99,999	PRODUCE , BYPRODUCT , REPACKAGING

Table 4-1. Facilities That Manufacture or Process Cadmium (continued)

FACILITY	LOCATION[a]	RANGE OF MAXIMUM AMOUNTS ON SITE IN POUNDS	ACTIVITIES AND USES
RIVER RECYCLING IND. INC.	CLEVELAND , OH	10,000 - 99,999	ARTICLE COMPONENT , REPACKAGING
BARTLETT-COLLINS GLASS CO.	SAPULPA , OK	10,000 - 99,999	ARTICLE COMPONENT
SHEFFIELD STEEL CORP.	SAND SPRINGS , OK	1,000 - 9,999	ARTICLE COMPONENT
SINCLAIR OIL CORP.	TULSA , OK	0 - 99	PRODUCE , BYPRODUCT
YAFFE IRON & METAL CO. INC.	MUSKOGEE , OK	10,000 - 99,999	ARTICLE COMPONENT
ZINC CORP. OF AMERICA	BARTLESVILLE , OK	1,000,000 - 9,999,999	PRODUCE , SALE/DISTRIBUTION , BYPRODUCT , REACTANT
CERDEC CORP.	WASHINGTON , PA	100,000 - 999,999	PRODUCE , IMPORT , ON-SITE USE/PROCESSING , SALE/DISTRIBUTION , FORMULATION COMPONENT ARTICLE COMPONENT , REPACKAGING
FERRO CORP.	PITTSBURGH , PA	10,000 - 99,999	REACTANT , FORMULATION COMPONENT
FRANKLIN SMELTING & REFINING	PHILADELPHIA , PA	10,000 - 99,999	PRODUCE , BYPRODUCT
GE CO.	BRIDGEVILLE , PA	10,000 - 99,999	ARTICLE COMPONENT
GENCORP INC.	JEANNETTE , PA	10,000 - 99,999	IMPORT , ON-SITE USE/PROCESSING , IMPURITY , FORMULATION COMPONENT
GENERAL BATTERY CORP.	READING , PA	100 - 999	PRODUCE , IMPORT , ON-SITE USE/PROCESSING , BYPRODUCT , FORMULATION COMPONENT
HPG INTL. INC.	MOUNTAIN TOP , PA	10,000 - 99,999	ARTICLE COMPONENT
INTERNATIONAL METALS	ELLWOOD CITY , PA	100,000 - 999,999	PRODUCE , SALE/DISTRIBUTION , BYPRODUCT , REACTANT
JOHNSTOWN CORP.	JOHNSTOWN , PA	0 - 99	ARTICLE COMPONENT
SPARTECH VY-CAL PLASTICS	CONSHOHOCKEN , PA	1,000 - 9,999	FORMULATION COMPONENT
WORLD RESOURCES CO.	POTTSVILLE , PA	1,000 - 9,999	IMPORT , ON-SITE USE/PROCESSING , FORMULATION COMPONENT , ARTICLE COMPONENT
ZINC CORP. OF AMERICA	MONACA , PA	100,000 - 999,999	PRODUCE , SALE/DISTRIBUTION , BYPRODUCT , IMPURITY
CUTLER-HAMMER DE PUERTO RICO	ARECIBO , PR	100 - 999	ARTICLE COMPONENT
COOLEY INC.	PAWTUCKET , RI	100 - 999	FORMULATION COMPONENT
ENGELHARD CORP.	WARWICK , RI	10,000 - 99,999	FORMULATION COMPONENT
NUCOR STEEL	DARLINGTON , SC	10,000 - 99,999	REACTANT
PIRELLI CABLE CORP.	ABBEVILLE , SC	1,000 - 9,999	ARTICLE COMPONENT
ALLIED-SIGNAL INC.	SPARTA , TN	10,000 - 99,999	FORMULATION COMPONENT , ARTICLE COMPONENT
AMERISTEEL CORP.	JACKSON , TN	100 - 999	PRODUCE , BYPRODUCT , REACTANT , ARTICLE COMPONENT
ASARCO INC.	EL PASO , TX	100,000 - 999,999	PRODUCE , IMPURITY
MARATHON POWER TECHS. CO.	WACO , TX	10,000 - 99,999	IMPORT , ON-SITE USE/PROCESSING , ARTICLE COMPONENT
NUCOR STEEL	JEWETT , TX	1,000 - 9,999	ANCILLARY/OTHER USE
SOUTHWEST CHEMICAL SERVICES	SEABROOK , TX	1,000 - 9,999	FORMULATION COMPONENT
SOUTHWESTERN PLATING CO. INC.	HOUSTON , TX	1,000 - 9,999	ARTICLE COMPONENT
TANDY WIRE & CABLE	FORT WORTH , TX	1,000 - 9,999	ARTICLE COMPONENT
GENEVA STEEL	VINEYARD , UT	10,000 - 99,999	FORMULATION COMPONENT
KENNECOTT UTAH COPPER	MAGNA , UT	10,000 - 99,999	PRODUCE , BYPRODUCT
NUCOR STEEL	PLYMOUTH , UT	1,000 - 9,999	PRODUCE , IMPURITY
DU PONT FRONT ROYAL PLANT	FRONT ROYAL , VA	10,000 - 99,999	FORMULATION COMPONENT
FEDERAL-MOGUL CORP.	BLACKSBURG , VA	1,000 - 9,999	ARTICLE COMPONENT
BOC GASES	VANCOUVER , WA	0 - 99	PRODUCE , IMPURITY
MASTER LOCK CO.	MILWAUKEE , WI	1,000 - 9,999	FORMULATION COMPONENT , ARTICLE COMPONENT

Source: TRI96 1998

[a] Post Office state abbreviations used

4.2 IMPORT/EXPORT

Imports of cadmium into the United States declined steadily from 1994 through 1998, dropping from 1,110 metric tons per year to an estimated 650 metric tons in 1998 (USGS 1999). In 1986, imports of cadmium metal for consumption increased significantly to 3,000 metric tons, but continually decreased into the 1990s. The principal supplying countries were Canada, Mexico, Belgium, and Australia (USGS 1999).

Export volumes of cadmium (reported as cadmium metal and cadmium in alloys, dross, flue dust, residues, and scrap) varied widely from year to year during the 1980s ranging from 10 tons in 1982 to about 450 metric tons in 1988 (ABMS 1994; Llewellyn 1988; NTP 1989, 1991; U.S. Bureau of Mines 1990). In the mid 1990s, exports also varied widely from 38 metric tons in 1993, to 1,450 metric tons in 1994, to 550 metric tons in 1997.

4.3 USE

Cadmium, its alloys, and its compounds are used in a variety of consumer and industrial materials. The use of cadmium compounds falls into five categories: active electrode materials in nickel-cadmium batteries (70% of total cadmium use); pigments used mainly in plastics, ceramics, and glasses (12%); stabilizers for polyvinyl chloride (PVC) against heat and light (17%); engineering coatings on steel and some nonferrous metals (8%); and components of various specialized alloys (2%) (Elinder 1992; IARC 1993; Thornton 1992; USGS 1997). Cadmium carbonate and cadmium chloride were used as fungicides for golf courses and lawns, but were banned by EPA in the late 1980s (Farm Chemicals Handbook 1997). The significance of cadmium chloride as a commercial product is declining; however, it is used in the preparation of cadmium sulfide, in the manufacture of special mirrors, and in dyeing and calico printing (IARC 1993). Cadmium-based colorants are used mainly in engineering plastics, ceramics, glasses and enamels. Cadmium sulfide and cadmium telluride are primarily used in solar cells and a variety of electronic devices which depend on cadmium’s semiconducting properties (IARC 1993; OECD 1994) The photoconductive and electroluminescent properties of cadmium sulfide have been applied in manufacturing a variety of consumer goods (IARC 1993).

Though cadmium metal consumption for batteries has grown steadily since the 1980s other uses of cadmium began declining in the mid 1990s. Pigement, stabilizer, coating, and alloy markets have peaked in

cadmium consumption (USGS 1997). Excessive exports from Bulgaria and Russia in 1997 caused a drop in the average price of cadmium from $1.84 per pound in 1995 to $0.51 per pound in 1997. Also, Ni-Cd batteries have been replaced in some markets by lithium-ion and nickel metal hydride batteries (USGS 1997). Regulations by local authorities have forced the recycling of cadmium in Ni-Cd batteries, further depressing the demand for primary cadmium metal (USGS 1999).

4.4 DISPOSAL

Cadmium-containing wastes are subject to regulations concerning their treatment, storage, and disposal (see Chapter 7) (EPA 1982a; HSDB 1994; U.S. Bureau of Mines 1990). Incineration of municipal wastes, particularly from older, poorly controlled facilities, is a potential environmental source of cadmium. In modern incineration plants, about 99.9% of cadmium was captured in boilers and control equipment (OECD 1994).

A range of physicochemical processes is available for treatment of cadmium in liquid waste process streams, including ion exchange, electrolysis, cementation, and adsorption. Both ion exchange and sulfide precipitation are used as alternate processes aimed at achieving low cadmium residuals in liquid wastes (UN 1985). Combining processes, for example, conducting the primary precipitation of cadmium as hydroxide followed by secondary precipitation of residual cadmium as sulfide, has also been adopted. The more general application of the sulfide precipitation technique, however, is constrained due to a tendency for formation of colloidal precipitate, the toxicity and odor of hydrogen sulfide, and the necessity to oxidize residual sulfide occurring in emissions prior to discharge (UN 1985).

The most widely used treatment process involves the alkaline precipitation of cadmium as hydroxide or basic salts (UN 1985). Removal of specific metal species during hydroxide precipitation is pH-dependent, and some components of the waste stream can influence the solubility of cadmium hydroxide. After filtration, the sludge formed from the conversion of soluble cadmium compounds to insoluble compounds can be deposited in a suitable landfill (UN 1985).

Various cadmium-bearing wastes are subject to aggressive leaching in refuse media, particularly under aerobic conditions (UN 1985). While liquid wastes are banned from land disposal, the leaching tendency is accentuated in the presence of brine solutions. Also, the mobility of cadmium in landfill conditions could be enhanced in the presence of mineral acids, which tend to solubilize cadmium compounds, or amine-

containing materials, which tend to complex cadmium ions. Waste containing mineral acids, cyanides, organic solvents, and amine-type substances should not be landfilled near cadmium-bearing wastes (UN 1985). According to the data compiled in the TRI (TRI961998), in 1996, about 3,100 pounds of cadmium were sent to publicly owned treatment works (POTWs). The data regarding manufacturing and processing facilities which reported releases to the environment indicate that 1,000 metric tons of cadmium-bearing wastes were transferred off-site, presumably for disposal or recovery (TRI961998). Releases to other environmental media are discussed in Chapter 5.

As an alternative to land disposal, scrap metals and batteries containing cadmium may be recycled (HSDB 1994; UN 1985). In the laboratory, a recommended method for recovering cadmium from small quantities of cadmium oxide wastes uses a minimum amount of concentrated nitric acid to form nitrates. The solution is evaporated in a hood to form a thin paste, then diluted with water and saturated with hydrogen sulfide. After the filtration, the precipitate is washed, dried, and returned to the supplier (UN 1985). No information was located regarding the quantity of cadmium currently being recycled in the United States.

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Small amounts of cadmium enter the environment from the natural weathering of minerals, forest fires, and volcanic emissions, but most is released by human activities such as mining and smelting operations, fuel combustion, disposal of metal-containing products, and application of phosphate fertilizer or sewage sludges (Elinder 1985a). It has been estimated that worldwide anthropogenic emissions of cadmium exceed natural ones by a factor close to ten (Elinder 1992; IARC 1993). Primary and secondary metal production, industrial applications, manufacture of phosphate fertilizers, waste incineration, and coal, wood, and oil combustion can all contribute cadmium to the atmosphere (Elinder 1985a). Recent pollutant emission control measures have reduced the output from these and other industrial sources in the United States.

Atmospheric cadmium is in the form of particulate matter, which may consist of very small particles if it is produced by combustion processes. The principal chemical species in air is cadmium oxide, although some cadmium salts, such as cadmium chloride, can enter the air, especially during incineration (IARC 1993). These are stable compounds that do not undergo significant chemical transformation. The chief fate of airborne cadmium is to be dispersed by the wind and, subsequently, deposited by wet or dry processes (Elinder 1985a).

In surface water and groundwater, cadmium can exist as the hydrated ion, or as ionic complexes with other inorganic or organic substances. While soluble forms may migrate in water, cadmium is relatively nonmobile in insoluble complexes or adsorbed to sediments. Similarly, cadmium in soil may exist in soluble form in soil water, or in insoluble complexes with inorganic and organic soil constituents. Cadmium in soil tends to be more available when the soil pH is low. Cadmium is taken up and retained by aquatic and terrestrial plants and is concentrated in the liver and kidney of animals that eat the plants (Elinder 1985a).

Human exposure to cadmium can result from consumption of food, drinking water, or incidental ingestion of soil or dust contaminated with cadmium; from inhalation of cadmium-containing particles from ambient air; from inhalation of cigarette smoke, which contains cadmium taken up by tobacco; or from working in an occupation involving exposure to cadmium fumes and dust (Elinder 1985a). For nonsmokers, ingestion

of food is the largest source of cadmium exposures. Most drinking water contains only very low levels of cadmium and is usually not an important route of exposure, although water may leach cadmium from plumbing. Concentrations of cadmium in ambient air are generally less than $5x10^{-6}$ mg/m^3, but concentrations up to $5x\ 10^{-4}$ mg/m^3 have been detected in air near cadmium-emitting facilities (Elinder 1985a).

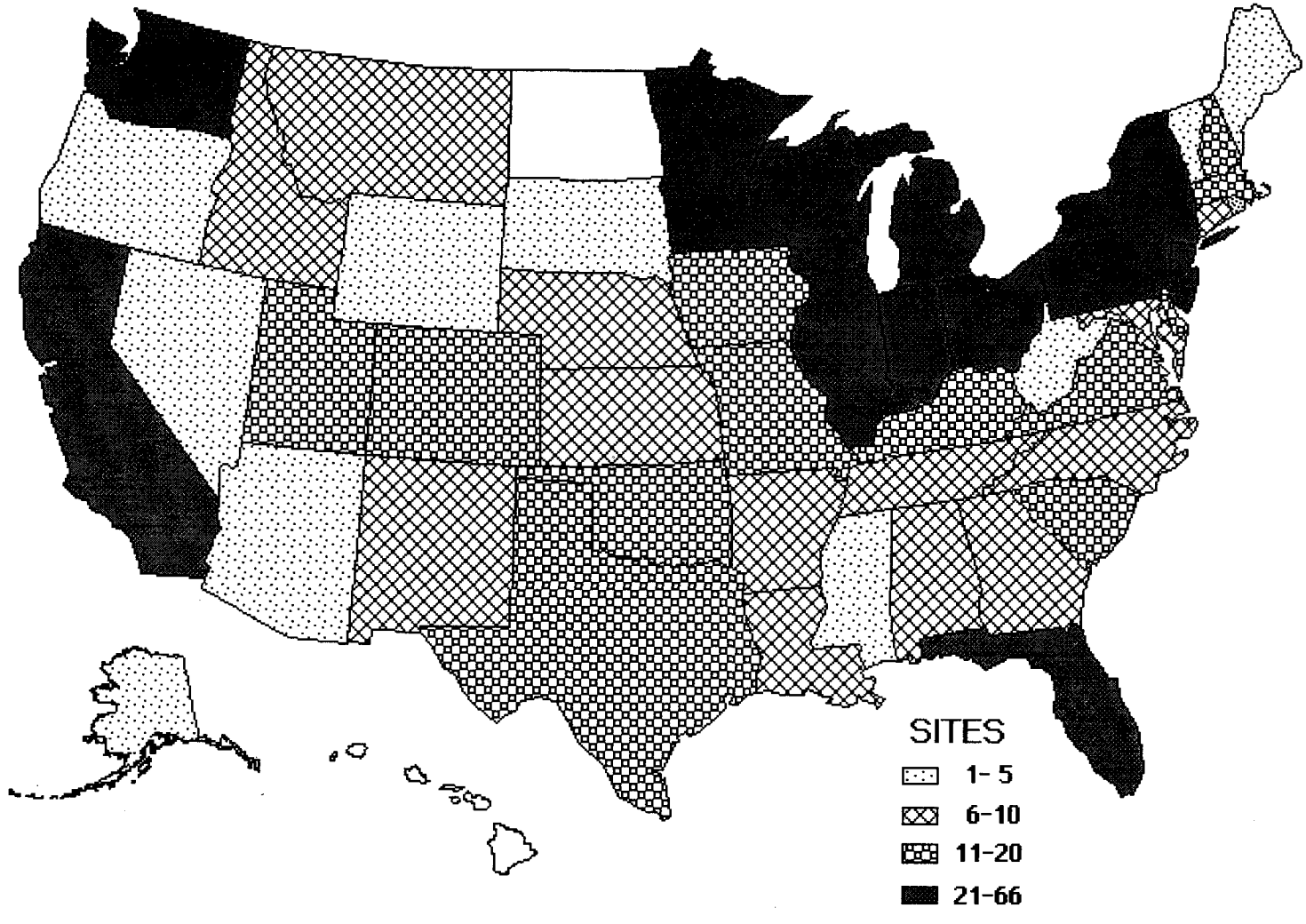
Levels of cadmium in soil may be increasing as a result of the application of municipal sludge or phosphate fertilizers, and this may result in greater human exposures from food chain accumulation in plants and animals. Dietary exposure may increase as acid precipitation lowers the soil pH. Grain and cereal products usually contribute the greatest percentage of dietary cadmium; potatoes, leafy vegetables, and root vegetables also contain relatively high levels. Organ meats (liver and kidney) and shellfish can also contribute to cadmium intake for individuals who consume large amounts of these items. Smoking is an important source of cadmium exposure and typically doubles the total daily absorption of cadmium (Elinder 1985a).

Cadmium has been identified in at least 776 of 1,467 current or former EPA National Priorities List (NPL) hazardous wastes sites (HazDat 1998). However, the number of sites evaluated for cadmium is not known. The frequency of these sites within the United States can be seen in Figure 5-l.

5.2 RELEASES TO THE ENVIRONMENT

According to the Toxics Release Inventory (TRI), in 1996, a total of 2,996,610 pounds (1,359,262 kg) of cadmium was released to the environment from 113 large processing facilities (TRI961998). Table 5-l lists amounts released from these facilities. In addition, an estimated 3,137 pounds (1,423 kg) were released by manufacturing and processing facilities to publicly owned treatment works (POTWs) and an estimated 2,273,306 pounds (1,031,172 kg) were transferred offsite (TRI961998). The TRI data should be used with caution since only certain types of facilities are required to report. Therefore, this is not an exhaustive list. Facilities are required to report data to TRI if they have 10 or more full-time employees, if the facility is classified under Standard Industrial Classification (SIC) codes 20 through 39, if the facility manufactures or processes more than 25,000 pounds of the chemical, or otherwise uses more than 10,000 pounds of the chemical in the calendar year (EPA 1995).

Figure 5-1. Frequency of NPL Sites with Cadmium Contamination



Derived from HazDat 1998

Table 5-1. Releases to the Environment from Facilities That Manufacture or Process Cadmium

			Reported amounts released in pounds per year [a]						
STATE [b]	CITY	FACILITY	AIR [c]	WATER	LAND	UNDERGROUND INJECTION	POTW TRANSFER	OFF-SITE WASTE TRANSFER	TOTAL ENVIRONMENT [d]
AL	ARAB	HALL CHEMICAL CO.	0	0	0	0	5	0	5
AL	BIRMINGHAM	BIRMINGHAM STEEL CORP.	1,073	0	0	0	0	21,312	22,385
AL	DECATUR	MONSANTO CO.	0	85	85	0	0	36,700	36,870
AL	TROY	SANDERS LEAD CO. INC.	10	250	250	0	250	1,074	1,834
AL	TUSCALOOSA	TUSCALOOSA STEEL CORP.	0	0	0	0	0	250	250
AR	BLYTHEVILLE	NUCOR-YAMATO STEEL CO.	2	0	0	0	0	43,181	43,183
AR	FORT SMITH	GNB TECHS. INC.	6	2	0	0	0	18,967	18,975
AZ	CLAYPOOL	CYPRUS MIAMI MINING CORP.	1,000	0	53,500	0	0	2,000	56,500
AZ	HAYDEN	ASARCO INC.	358	0	4,083	0	5	48,587	53,033
AZ	SAN MANUEL	BHP COPPER METALS CO.	500	0	35,894	0	0	30,284	66,678
CA	COMPTON	EME INC.	0	0	0	0	4	0	4
CA	PACOIMA	BURBANK PLATING SERVICES CORP.	5	0	0	0	250	5,100	5,355
CA	SUN VALLEY	ALERT PLATING CO.	10	0	0	0	5	798	813
CO	COLORADO SPRINGS	EAGLE-PICHER IND. INC.	248	0	0	0	0	16,926	17,174
CT	ANSONIA	ANSONIA COPPER & BRASS INC.	390	1	0	0	0	1,891	2,282
CT	FAIRFIELD	HANDY & HARMAN	45	3	0	0	0	8,700	8,748
CT	STRATFORD	FLOW POLYMERS INC.	10	0	0	0	0	2,346	2,356
CT	STRATFORD	SYNTHETIC PRODS. CO.	255	0	0	0	0	1,872	2,127
FL	ALACHUA	EVEREADY BATTERY CO. INC.	971	5	0	0	0	95,200	96,176
FL	JACKSONVILLE	JEFFERSON SMURFIT CORP.	0	0	0	0	0	650	650
GA	ATLANTA	ARMSTRONG GLASS CO. INC.	0	0	0	0	0	5	5
GA	VALDOSTA	SAFT AMERICA INC.	29	7	0	0	6	142,557	142,599
IA	BLOOMFIELD	BLOOMFIELD FNDY. INC.	10	0	0	0	0	5	15
ID	POCATELLO	FMC CORP.	340	0	337,964	0	0	37	338,341
IL	CHICAGO HEIGHTS	CALUMET STEEL CO.	7	0	0	0	1	1,700	1,708
IL	ELK GROVE VILLAGE	API IND. INC.	5	0	0	0	250	43,000	43,255
IL	ELK GROVE VILLAGE	THREE J'S IND. INC.	10	0	0	0	5	1,100	1,115
IL	HARTFORD	CHEMETCO INC.	1,000	5	0	0	0	0	1,005
IL	KANKAKEE	GNB TECHS. INC.	3	0	0	0	0	4,896	4,899
IL	SAUGET	BIG RIVER ZINC CORP.	1,332	0	0	0	5	18,991	20,328
IN	EDINBURGH	UNITED TECHS. AUTOMOTIVE INC.	5	0	0	0	0	2,250	2,255
IN	HAMMOND	JUPITER ALUMINUM CORP.	0	0	0	0	0	2,107	2,107
IN	MOUNT VERNON	GE PLASTICS CO.	27	0	0	0	0	2,954	2,981
KS	HOISINGTON	ESSEX GROUP INC.	0	0	0	0	0	5,850	5,850
KY	JEFFERSONTOWN	CONDEA VISTA CO.	122	0	0	0	22	50	194
KY	LOUISVILLE	ENGELHARD CORP.	755	0	50,700	0	250	50,750	102,455
KY	WILDER	NEWPORT STEEL CORP.	16	0	0	0	0	2,900	2,916
LA	BATCHELOR	NAN YA PLASTICS CORP. AMERICA	0	0	0	0	0	5	5
LA	SHREVEPORT	LIBBEY GLASS INC.	0	0	1,878	0	188	1,878	3,944
MA	ATTLEBORO	ATTLEBORO REFINING CO. INC.	500	0	0	0	0	14,864	15,364
MA	ATTLEBORO	CHEMET CORP.	3	0	0	0	1	6,140	6,144
MD	BALTIMORE	SCM GLIDCO ORGANICS CORP.	5	7	0	0	13	38,105	38,130
MI	DEARBORN	ROUGE STEEL CO.	250	250	0	0	0	7,226	7,726
MI	DETROIT	AJAX METAL PROCESSING INC.	0	0	0	0	250	1,205	1,455
MI	JACKSON	DIECAST CORP.	250	0	0	0	0	500	750

Table 5-1. Releases to the Environment from Facilities That Manufacture or Process Cadmium (continued)

			Reported amounts released in pounds per year [a]						
STATE [b]	CITY	FACILITY	AIR [c]	WATER	LAND	UNDERGROUND INJECTION	POTW TRANSFER	OFF-SITE WASTE TRANSFER	TOTAL ENVIRONMENT [d]
MI	JACKSON	ELM PLATING CO.	5	0	0	0	5	10	20
MO	ANNAPOLIS	ASARCO INC.	1,312	2	7,520	0	0	0	8,834
MO	HERCULANEUM	DOE RUN CO.	8,871	13	5,703	0	49	0	14,636
MO	SAINT PETERS	M. A. HANNA COLOR	48	0	0	0	0	957	1,005
MS	CORINTH	IPC CORINTH DIV. INC.	1	0	0	0	0	223	224
MS	PRAIRIE	NORTH AMERICAN PLASTICS INC.	5	0	0	0	0	0	5
MT	EAST HELENA	ASARCO INC.	9,773	190	22,108	0	3	174,637	206,711
NC	PINE HALL	KOBE COPPER PRODS. INC.	12	0	2,100	0	0	52,500	54,612
NE	FAIRBURY	AMERICAN MICROTRACE CORP.	0	77	0	0	0	24,738	24,815
NE	LINCOLN	YANKEE HILL BRICK MFG. CO.	0	0	3,000	0	0	0	3,000
NE	OMAHA	LUCENT TECHS. INC.	1	0	0	0	2	57	60
NJ	MILLVILLE	DURAND GLASS MFG. CO.	10	0	0	0	0	333	343
NJ	NEW BRUNSWICK	AKCROS CHEMICALS AMERICA	5	0	0	0	1	496	502
NJ	RIVERSIDE	METAL IND. CORP.	5	0	0	0	0	0	5
NJ	SOUTH PLAINFIELD	DEGUSSA CORP.	4	0	0	0	5	0	9
NJ	UNION	M.C. CANFIELD INC.	2	0	0	0	5	1	8
NJ	WOODBRIDGE	GENTEK BUILDING PRODS.	0	0	0	0	0	8	8
NM	HURLEY	CHINO MINES CO.	11,533	0	106,581	0	0	0	118,114
NY	BROOKLYN	BELMONT METALS INC.	250	0	0	0	0	0	250
NY	BROOKLYN	NEY SMELTING & REFINING CO.	1	0	0	0	0	0	1
NY	HERKIMER	H. M. QUACKENBUSH INC.	0	0	0	0	250	8,109	8,359
NY	*HORSEHEADS*	*THOMAS & BETTS*	0	0	0	0	5	4,256	4,261
NY	SIDNEY	AMPHENOL CORP.	0	48	0	0	0	3,976	4,024
OH	CLEVELAND	BARKER PRODS.	0	0	800	0	16	800	1,616
OH	CLEVELAND	ERIEVIEW METAL TREATING CO.	0	0	0	0	5	14,672	14,677
OH	CLEVELAND	FERRO CORP.	123	0	0	0	17	253	393
OH	CLEVELAND	N & W METAL FINISHING INC.	0	0	0	0	250	19,203	19,453
OH	CLEVELAND	RIVER RECYCLING IND. INC.	15	0	0	0	0	753	768
OH	DAYTON	HOHMAN PLATING & MFG. INC.	500	0	0	0	60	2,490	3,050
OH	DOVER	DOVER CHEMICAL CORP.	39	0	0	0	0	1,481	1,520
OH	MIDDLETOWN	AK STEEL CORP.	10	0	0	0	0	0	10
OH	MINERVA	GENERAL COLOR & CHEMICAL CO.	1,980	0	0	0	250	0	2,230
OH	TOLEDO	LIBBEY GLASS INC.	0	1	0	0	52	2,558	2,611
OH	WALTON HILLS	FERRO CORP.	500	0	0	0	9	814	1,323
OH	YOUNGSTOWN	NORTH STAR STEEL	67	0	0	0	3	6,586	6,656
OK	BARTLESVILLE	ZINC CORP. OF AMERICA	1	0	40	82	0	564,700	564,823
OK	MUSKOGEE	YAFFE IRON & METAL CO. INC.	0	0	0	0	0	27,604	27,604
OK	*SAND SPRINGS*	*SHEFFIELD STEEL CORP.*	*250*	*0*	*0*	*0*	*0*	*10,392*	*10,642*
OK	SAPULPA	BARTLETT-COLLINS GLASS CO.	0	0	0	0	0	1,958	1,958
OK	TULSA	SINCLAIR OIL CORP.	0	5	5	0	0	0	10
PA	BRIDGEVILLE	GE CO.	453	100	0	0	0	37,300	37,853
PA	ELLWOOD CITY	INTERNATIONAL METALS	3,479	2,745	0	0	5	164,000	170,229
PA	JEANNETTE	GENCORP INC.	67	2	0	0	0	2,187	2,256
PA	JOHNSTOWN	JOHNSTOWN CORP.	0	0	0	0	0	10	10
PA	MONACA	ZINC CORP. OF AMERICA	593	30	0	0	0	142,736	143,359

Table 5-1. Releases to the Environment from Facilities That Manufacture or Process Cadmium (continued)

			Reported amounts released in pounds per year [a]						
STATE [b]	CITY	FACILITY	AIR [c]	WATER	LAND	UNDERGROUND INJECTION	POTW TRANSFER	OFF-SITE WASTE TRANSFER	TOTAL ENVIRONMENT [d]
PA	MOUNTAIN TOP	HPG INTL. INC.	243	0	0	0	0	0	243
PA	PHILADELPHIA	FRANKLIN SMELTING & REFINING	1,000	250	0	0	0	0	1,250
PA	PITTSBURGH	FERRO CORP.	10	0	0	0	5	40	55
PA	POTTSVILLE	WORLD RESOURCES CO.	10	0	0	0	5	0	15
PA	READING	GENERAL BATTERY CORP.	9	37	0	0	0	6,150	6,196
PA	WASHINGTON	CERDEC CORP.	243	4	0	0	9	3,374	3,630
PR	ARECIBO	CUTLER-HAMMER DE PUERTO RICO	2,732	0	0	0	0	0	2,732
RI	WARWICK	ENGELHARD CORP.	0	0	0	0	1	603	604
SC	ABBEVILLE	PIRELLI CABLE CORP.	0	0	0	0	0	4,613	4,613
SC	DARLINGTON	NUCOR STEEL	500	0	0	0	0	24,752	25,252
TN	JACKSON	AMERISTEEL CORP.	48	5	0	0	0	9,939	9,992
TN	SPARTA	ALLIED-SIGNAL INC.	5	0	0	0	0	5	10
TX	EL PASO	ASARCO INC.	646	0	255	0	5	135,750	136,656
TX	FORT WORTH	TANDY WIRE & CABLE	0	0	0	0	0	6	6
TX	HOUSTON	SOUTHWESTERN PLATING CO. INC.	0	0	0	0	5	4,610	4,615
TX	JEWETT	NUCOR STEEL	114	0	1,000	0	0	21,530	22,644
TX	WACO	MARATHON POWER TECHS. CO.	10	250	0	0	600	42,800	43,660
UT	MAGNA	KENNECOTT UTAH COPPER	255	250	24,005	0	0	5,350	29,860
UT	PLYMOUTH	NUCOR STEEL	115	0	1,046	0	0	36,201	37,362
UT	VINEYARD	GENEVA STEEL	2	0	750	0	0	0	752
VA	BLACKSBURG	FEDERAL-MOGUL CORP.	14	0	0	0	4	10,071	10,089
WA	VANCOUVER	BOC GASES	0	0	761	0	0	761	1,522
WI	MILWAUKEE	MASTER LOCK CO.	10	0	0	0	1	11,040	11,051
		TOTALS	55,433	4,624	660,028	82	3,137	2,273,306	2,996,610

Source: TRI96 1998

[a] Data in TRI are maximum amounts released by each facility

[b] Post office state abbreviations used

[c] The sum of fugitive and stack releases are included in releases to air by a given facility

[d] The sum of all releases of the chemical to air, land, and water, and underground injection wells; and transfers off-site by a given facility

POTW = publicly owned treatment works

Additional releases of cadmium to the environment occur from natural sources and from processes such as combustion of fossil fuel, incineration of municipal or industrial wastes, or land application of sewage sludge or fertilizer (EPA 1985a). Quantitative information on releases of cadmium to specific environmental media is discussed below.

5.2.1 Air

Cadmium is released to the atmosphere from both natural and anthropogenic sources. Cadmium is widely distributed in the earth's crust and, consequently, may be released to the air from entrainment of dust particles, volcanic eruptions, or other natural phenomena (EPA 1985a). However, industrial activities are the main sources of cadmium release to air (EPA 1985a, 1985d), and emissions from anthropogenic sources have been found to exceed those of natural origin by an order of magnitude (IARC 1993). Major industrial sources of cadmium emissions include zinc, lead, copper, and cadmium smelting operations; coal and oil-fired boiler; pigment manufacturing plants; and municipal and sewage sludge incinerators (EPA 1985d; Wilber et al. 1992). It has been suggested that coal and oil used in classical thermal power plants are responsible for 50% of the total cadmium emitted to the atmosphere (Thornton 1992). Emission rates of cadmium from solid waste incinerators have been found to range from 20 to 2,000 $\mu g/m^3$ from the stacks of traditional incinerators and from 10 to 40 $\mu g/m^3$ from advanced incinerators. These emissions could result in deposition rates of l-40 and 0.02-0.8 $\mu g/m^3$ per day, respectively (IARC 1993). Additional sources that contribute negligible amounts of cadmium are rubber tire wear, motor oil combustion, cement manufacturing, and fertilizer and fungicide application (Wilber et al. 1992). Total atmospheric emissions of cadmium were estimated to be 1.4 million pounds annually in the early 1980s (EPA 1985d), with about 400,000 pounds from smelting operations, manufacturing plants, and incinerators, and 1 million pounds from fossil fuel combustion. Atmospheric cadmium occurs mainly in the forms of cadmium oxide and cadmium chloride (NTP 1991). According to TRI96 (1998), an estimated total of 55,433 pounds (25,144 kg) of cadmium, amounting to 1.8% of the total environmental release, was discharged to the air from manufacturing and processing facilities in the United States in 1996. Table 5-1 lists amounts released from these facilities. The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list. The total atmospheric release reported in 1996 is higher than the release of 15,290 pounds reported in 1993, but is lower than the release of 120,000 pounds reported in 1988.

Atmospheric emissions of cadmium are being reduced by controls necessary to meet the requirements of particulate emissions regulations (EPA 1985d). In addition, EPA has proposed risk-based regulations for cadmium emissions from hazardous waste incinerators (EPA 1990a). Therefore, although there may be an increase in fossil fuel combustion and waste incineration, it does not appear likely that overall cadmium emissions to air will increase substantially.

There is a potential for release of cadmium to air from hazardous waste sites. Cadmium has been detected in air samples collected at 33 of the 776 NPL hazardous waste sites where cadmium has been detected in some environmental medium (HazDat 1998). The HazDat information used includes data from NPL sites only.

5.2.2 Water

Cadmium may be released to water by natural weathering processes, by discharge from industrial facilities or sewage treatment plants, or by leaching from landfills or soil (EPA 1981, 1985a; IJC 1989). Cadmium may also leach into drinking water supplies from pipes in the distribution system (Elinder 1985a). According to TRI96 (1998), an estimated total of 4,624 pounds (2,097 kg) of cadmium, amounting to 0.2% of the total environmental release, was discharged to water from manufacturing and processing facilities in the United States in 1996. However, an additional 3,137 pounds (1,423 kg) were released indirectly to POTWs and some of this volume may have been released to surface water. Only 82 pounds (37 kg) were released to underground injection wells. The TRI data should be used with caution since only certain facilities are required to report. This is not an exhaustive list.

Smelting of nonferrous metal ores has been estimated to be the largest anthropogenic source of cadmium released into the aquatic environment. Cadmium contamination can result from entry into aquifers of mine drainage water, waste water, tailing pond overflow, and rainwater runoff from mine areas (IARC 1993). The upper Clark Fork River in Montana is contaminated with large amounts of cadmium from past mining activities between 1880 and 1972. While mining wastes are no longer released into the river, an estimated 14.5 million m^3 of tailings have been incorporated into the river bed, floodplain, and reservoir sediments (Canfield et al. 1994). Other human sources include spent solutions from plating operations and phosphate fertilizers. Cadmium constitutes up to 35 mg/kg of phosphorous pentoxide in the United States (IARC 1993). Atmospheric fallout of cadmium to aquatic systems is another major source of cadmium to the environment (IARC 1993; Muntau and Baudo 1992).

A large proportion of the cadmium load in the aquatic environment is due to diffuse pollution originating from many different sources rather than from point sources. In the estuarine portion of the Hudson River, it has been found that more cadmium was released from agricultural and urban run-off than from industrial and municipal sewage treatment plants (Muntau and Baudo 1992).

There is also a potential for release of cadmium to water from hazardous waste sites. Cadmium has been detected in surface water samples collected at 263 of the 776 NPL hazardous waste sites, in leachate samples collected at 100 of the 776 hazardous waste sites, and in groundwater samples collected at 541 of the 776 NPL hazardous waste sites where cadmium has been detected in some environmental medium (HazDat 1998). The HazDat information used includes data from NPL sites only.

5.2.3 Soil

Land disposal of cadmium-containing wastes (including batteries), land application of sewage sludge, and the use of phosphate fertilizers are the principal sources of cadmium releases to soil (Elinder 1985a; EPA 1985d; IARC 1993). According to TRI96 (1998), an estimated total of 660,028 pounds (299,389 kg) of cadmium, amounting to 22.0% of the total environmental release, was discharged to land from manufacturing and processing facilities in the United States in 1996. The total cadmium released to land in 1996 is significantly higher than the release of 56,665 pounds reported in 1993. Some of the estimated 2,273,306 pounds of cadmium waste transferred offsite also may be ultimately disposed to land. The TRI data should be used with caution since only certain facilities are required to report. This is not an exhaustive list.

EPA estimated that about 31% of the 11 billion pounds of sewage sludge produced annually in the United States is landspread (EPA 1985a). Estimated cadmium concentrations in sewage sludge range from less than 1 μg/g to more than 1,000 μg/g (EPA 1985a). Although EPA has set limits (EPA 1993) on the cadmium content of sludge applied to land (maximum permitted cadmium concentration of 85 mg/kg in sewage sludge; maximum cadmium concentration of 39 mg/kg in “clean” sewage sludge; maximum annual cadmium loading of 1.9 kg-ha^{-1}·yr^{-1}; and maximum cumulative cadmium loading of 39 kg/ha), significant amounts of cadmium are still likely to be transferred to soil by this practice.

Phosphate fertilizers are a major source of cadmium input to agricultural soils (EPA 1985a). The natural cadmium concentration in phosphates ranges from 3 to 100 μg/g (EPA 1985a; Singh 1994). The

concentration of cadmium in phosphate fertilizers ranges from 0.05 to 170 mg/kg (ppm) (Singh 1994). It is estimated that 880,000 pounds of phosphate fertilizer were used in the United States in 1980 (EPA 1985a). Continuous fertilization with a high rate of triple super-phosphate (1,175 kg P·ha-1· yr^{-1}) for a period of 36 years resulted in a 14-fold increase in cadmium content of surface soils (Singh 1994).

Wet and dry deposition of cadmium from the atmosphere may also contribute sizable amounts of cadmium to soil in the areas surrounding sources of atmospheric emissions, such as incinerators and vehicular traffic, which may release cadmium from burned fuel and tire wear (EPA 1985a; Mielke et al. 1991).

There is also a potential for release of cadmium to soil from hazardous waste sites. Cadmium has been detected in soil samples collected at 433 of the 776 NPL hazardous waste sites, in soil gas samples collected at 1 of the 776 NPL hazardous waste sites, and in sediment samples collected at 274 of the 776 NPL hazardous waste sites where cadmium has been detected in some environmental medium (HazDat 1998). The HazDat information used includes data from NPL sites only.

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

Cadmium and cadmium compounds have negligible vapor pressures (see Table 3-2), but may exist in air as suspended particulate matter derived from sea spray, industrial emissions, combustion of fossil fuels, or the erosion of soils (Elinder 1985a; Keitz 1980). In processes that involve extremely high temperatures (e.g., the iron and steel industries), cadmium can volatilize and be emitted as a vapor (Wilber et al. 1992). Cadmium emitted to the atmosphere from combustion processes is usually associated with very small particulates that are in the respirable range (<10 μm) and are subject to long-range transport. These cadmium pollutants may be transported from a hundred to a few thousand kilometers and have a typical atmospheric residence time of about l-10 days before deposition occurs (Keitz 1980). Larger cadmium containing particles from smelters and other pollutant sources are also removed from the atmosphere by gravitational settling, with substantial deposition in areas downwind of the pollutant source. Cadmium deposition in urban areas is about one order of magnitude higher than in rural areas of the United States (Keitz 1980).

Cadmium-containing particulates may dissolve in atmospheric water droplets and be removed from air by wet deposition. The reported median concentration of cadmium in precipitation is about 0.7 μg/L in rural and urban areas (Keitz 1980). Scudlark et al. (1994) measured an average atmospheric wet flux of cadmium to 2 sites in the Chesapeake Bay area of 48 μg m^{-2} yr^{-1} .

Cadmium is more mobile in aquatic environments than most other heavy metals (e.g., lead). In most natural surface waters, the affinities of complexing ligands for cadmium generally follow the order of humic acids > CO_3^{2-} > OH^- ≥ Cl^- ≥ SO_4^{2-} (Callahan et al. 1979). In unpolluted natural waters, most cadmium transported in the water column will exist in the dissolved state as the hydrated ion $Cd(H_2O)_6^{2+}$. Minor amounts of cadmium are transported with the coarse particulates, and only a small fraction is transported with the colloids. In unpolluted waters, cadmium can be removed from solution by exchange of cadmium for calcium in the lattice structure of carbonate minerals (Callahan et al. 1979). In polluted or organic-rich waters, adsorption of cadmium by humic substances and other organic complexing agents plays a dominant role in transport, partitioning, and remobilization of cadmium (Callahan et al. 1979). Cadmium concentration in water is inversely related to the pH and the concentration of organic material in the water (Callahan et al. 1979). Because cadmium exists only in the +2 oxidation state in water, aqueous cadmium is not strongly influenced by the oxidizing or reducing potential of the water. However, under reducing conditions, cadmium may form cadmium sulfide, which is poorly soluble and tends to precipitate (EPA 1983c; McComish and Ong 1988). Free (ionic) cadmium seems to be the toxic form and becomes much more prevalent at low salinity (Sprague 1986). Cadmium has a relatively long residence time in aquatic systems. In Lake Michigan, a mean residence time of 4-10 years was calculated for cadmium compared to 22 years calculated for mercury (Wester et al. 1992).

Precipitation and sorption to mineral surfaces, hydrous metal oxides, and organic materials are the most important processes for removal of cadmium to bed sediments. Humic acid is the major component of sediment responsible for adsorption. Sorption increases as the pH increases (Callahan et al. 1979). Sediment bacteria may also assist in the partitioning of cadmium from water to sediments (Burke and Pfister 1988). Both cadmium-sensitive and cadmium-resistant bacteria reduced the cadmium concentration in the water column from 1 ppm to between 0.2 and 0.6 ppm, with a corresponding increase in cadmium concentration in the sediments in the simulated environment (Burke and Pfister 1988). Studies indicate that concentrations of cadmium in sediments are at least one order of magnitude higher than in the overlying water (Callahan et al. 1979). The mode of sorption of cadmium to sediments is important in determining its disposition to remobilize. Cadmium associated with carbonate minerals, precipitated as stable solid

compounds or co-precipitated with hydrous iron oxides, is less likely to be mobilized by resuspension of sediments or biological activity. Cadmium that is adsorbed to mineral surfaces such as clay, or to organic materials, is more easily bioaccumulated or released in the dissolved state when the sediment is disturbed (Callahan et al. 1979). Cadmium may redissolve from sediments under varying ambient conditions of pH, salinity, and redox potential (Callahan et al. 1979; Eisler 1985; Feijtel et al. 1988; Muntau and Baudo 1992). Cadmium is not known to form volatile compounds in the aquatic environment, so partitioning from water to the atmosphere does not occur (Callahan et al. 1979).

Debusk et al. (1996) studied the retention and compartmentalization of lead and cadmium in wetland microcosms. Differences between measured concentrations in inflow and outflow samples indicated that approximately half of the added cadmium was retained in the wetland microcosms. Experiments showed that nearly all trace metals were present in the sediments as sulfides, limiting their bioavailability and toxicity. The results of their analyses and a lack of noticeable biological effects suggested that in wetlands containing organic sediments, the sediment chemistry dominates cycling of the trace metals,

In soils, pH, oxidation-reduction reactions, and formation of complexes are important factors affecting the mobility of cadmium (Bermond and Bourgeois 1992; Herrero and Martin 1993). Cadmium can participate in exchange reactions on the negatively charged surface of clay minerals. In acid soils, the reaction is reversible. However, adsorption increases with pH and may become irreversible (Herrero and Martin 1993). Cadmium also may precipitate as insoluble cadmium compounds, or form complexes or chelates by interaction with organic matter. Available data suggest that organic matter is more effective than inorganic constituents in keeping cadmium unavailable (McBride 1995). Examples of cadmium compounds found in soil are $Cd_3(PO_4)_2$, $CdCO_3$, and $Cd(OH)_2$ (Herrero and Martin 1993). These compounds are formed as the pH rises. It has been found that about 90% of cadmium in soils remains in the top 15 cm (Anonymous 1994).

The mobility and plant availability of cadmium in wetland soils are substantially different from upland soils. Cadmium tends to be retained more strongly in wetland soils and is more available to plants under upland conditions (Gambrell 1994). Debusk et al. (1996) compared heavy metal uptake by cattails and duckweed wetland microcosms and found that duckweed, on a whole-plant basis, accumulates cadmium more effectively than cattail does. The potential cadmium removal rate for duckweed is 2-4 mg Cd/m^2/day.

Cadmium in soils may leach into water, especially under acidic conditions (Callahan et al. 1979; Elinder 1985a). Roy et al. (1993) demonstrated that Cl complexation in the leachate of ash from a municipal solid waste incinerator can result in a decrease in cadmium sorption by two common clays, kaolinite and illite. They also found that cationic competitive sorption enhances mobility in soils. Cadmium-containing soil particles may also be entrained into the air or eroded into water, resulting in dispersion of cadmium into these media (EPA 1985a). Contamination of soil by cadmium is of concern because the cadmium is taken up efficiently by plants and, therefore, enters the food chain for humans and other animals. A low soil pH, which is becoming prevalent in many areas of the world due to acid rain, increases the uptake of cadmium by plants (Elinder 1992).

Aquatic and terrestrial organisms bioaccumulate cadmium (Handy 1992a, 1992b; Kuroshima 1992; Naqui and Howell 1993; Roseman et al. 1994; Suresh et al. 1993). Cadmium concentrates in freshwater and marine animals to concentrations hundreds to thousands of times higher than in the water (Callahan et al. 1979). Reported bioconcentration factors (BCFs) range from 113 to 18,000 for invertebrates (EPA 1985d; van Hattum et al. 1989), from 3 to 4,190 for fresh water aquatic organisms (ASTER 1995), and from 5 to 3,160 for saltwater aquatic organisms (ASTER 1994). Bioconcentration in fish depends on the pH and the humus content of the water (John et al. 1987). Because of their high ability to accumulate metals, some aquatic plants have been suggested for use in pollution control. For example, it has been suggested that the rapidly-growing water hyacinth *Eichhornia crussipes* could be used to remove cadmium from domestic and industrial effluents (Ding et al. 1994; Muntau and Baudo 1992).

The data indicate that cadmium bioaccumulates in all levels of the food chain. Cadmium accumulation has been reported in grasses and food crops, and in earthworms, poultry, cattle, horses, and wildlife (Alloway et al. 1990; Beyer et al. 1987; Gochfeld and Burger 1982; Kalac et al. 1996; Munshower 1977; Ornes and Sajwan 1993; Rutzke et al. 1993; Sileo and Beyer 1985; Vos et al. 1990). The metal burden of a crop depends on uptake by the root system, direct foliar uptake and translocation within the plant, and surface deposition of particulate matter (Nwosu et al. 1995). In general, cadmium accumulates in the leaves of plants and, therefore, is more of a risk in leafy vegetables grown in contaminated soil than in seed or root crops (Alloway et al. 1990). He and Singh (1994) report that, for plants grown in the same soil, accumulation of cadmium decreased in the order: leafy vegetables > root vegetables > grain crops. Alloway et al. (1990) also demonstrated that uptake of cadmium decreased in the order: lettuces, cabbages, radishes, and carrots. Nwosu et al. (1995) investigated the uptake of Cd and Pb in lettuce and radish grown in loam soil spiked with known mixtures of $CdCl_2$ and $Pb(NO_3)_2$. They found that the mean uptake

of Cd by lettuce and radish increased as the concentrations of Cd and Pb in the soil increased. Their results supported previous findings that cadmium is absorbed by passive diffusion and translocated freely in the soil. The observed decline in Cd uptake by lettuce at 400 mg/kg could be attributed to saturation of the active binding sites on the plant root system or by early toxicological responses of the plant root. The study also supported earlier findings that radish did not accumulate as much cadmium as lettuce.

Some studies have concluded that soil pH is the major factor influencing plant uptake of cadmium from soils (Smith 1994). Liming of soil raises the pH, increasing cadmium adsorption to the soil and reducing bioavailability (He and Singh 1994; Thornton 1992). One study found that in peeled potato tubers, potato peelings, oat straw, and ryegrass, cadmium concentrations generally decreased as simple linear functions of increasing soil pH over the range of pH values measured (pH 3.9-7.6) (Smith 1994). Soil type also affects uptake of cadmium by plants. For soils with the same total cadmium content, cadmium has been found to be more soluble and more plant-available in sandy soil than in clay soil (He and Singh 1994). Similarly, cadmium mobility and bioavailability are higher in noncalcareous than in calcareous soils (Thornton 1992).

Since cadmium accumulates largely in the liver and kidneys of vertebrates and not in the muscle tissue (Harrison and Klaverkamp 1990; Sileo and Beyer 1985; Vos et al. 1990), and intestinal absorption of cadmium is low, biomagnification through the food chain may not be significant (Sprague 1986). In a study of marine organisms from the Tyrrhenian Sea, no evidence of cadmium biomagnification was found along pelagic or benthic food webs (Bargagli 1993). Although some data indicate increased cadmium concentrations in animals at the top of the food chain, comparisons among animals at different trophic levels are difficult, and the data available on biomagnification are not conclusive (Beyer 1986; Gochfeld and Burger 1982). Nevertheless, uptake of cadmium from soil by feed crops may result in high levels of cadmium in beef and poultry (especially in the liver and kidneys). This accumulation of cadmium in the food chain has important implications for human exposure to cadmium, whether or not significant biomagnification occurs.

Boularbah et al. (1992) isolated 6 cadmium-resistant bacterial strains from a soil receiving dredged sediments and containing 50 mg Cd/kg. The isolates tolerated higher cadmium concentrations than the control strain and accumulated cadmium at concentrations ranging from 0 to 100 mg/L. One of the isolates, Bacillus brevis, was found to be the most resistant to cadmium, with the ability to accumulate up to 70 mg Cd/g of cells dry weight (d/w), and may have some use in reclamation of metal-contaminated soils.

5.3.2 Transformation and Degradation

5.3.2.1 Air

Little information is available on the atmospheric reaction of cadmium (Keitz 1980). The common cadmium compounds found in air (oxide, sulfate, chloride) are stable and not subject to photochemical reactions (Keitz 1980). Cadmium sulfide may photolyze to cadmium sulfate in aqueous aerosols (Konig et al. 1992). Transformation of cadmium among types of compounds in the atmosphere is mainly by dissolution in water or dilute acids (Keitz 1980).

5.3.2.2 Water

In fresh water, cadmium is present primarily as the cadmium(+2) ion and Cd(OH), and CdCO, complexes, although at high concentrations of organic material, more than half may occur in organic complexes (McComish and Ong 1988; NTP 1991). Some cadmium compounds, such as cadmium sulfide, cadmium carbonate, and cadmium oxide, are practically insoluble in water. However, water-insoluble compounds can be changed to water-soluble salts by interaction with acids or light and oxygen. For example, aqueous suspensions of cadmium sulfide can gradually photoxidize to soluble cadmium (IARC 1993). Cadmium complexation with chloride ion increases with salinity until, in normal seawater, cadmium exists almost entirely as chloride species ($CdCl^+$, $CdCl_2$, $CdCl\ 3^-$) with a minor portion as Cd^{2+} (NTP 1991). In reducing environments, cadmium precipitates as cadmium sulfide (McComish and Ong 1988). Photolysis is not an important mechanism in the aquatic fate of cadmium compounds (EPA 1983c), nor is biological methylation likely to occur (Callahan et al. 1979).

5.3.2.3 Sediment and Soil

Transformation processes for cadmium in soil are mediated by sorption from and desorption to water, and include precipitation, dissolution, complexation, and ion exchange (McComish and Ong 1988). Important factors affecting transformation in soil include the cation exchange capacity, the pH, and the content of clay minerals, carbonate minerals, oxides, organic matter, and oxygen (McComish and Ong 1988).

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to cadmium depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. In reviewing data on cadmium levels monitored in the environment, it should also be noted that the amount of the cadmium compound identified analytically is not necessarily equivalent to the amount that is bioavailable.

5.4.1 Air

Mean levels of cadmium in ambient air range from less than $1x10^{-6}$ mg/m^3 in remote areas to $3x10^{-6}$-4xl0^{-5} mg/m^3 in U.S. urban areas (Davidson et al. 1985; Eisler 1985; Elinder 1985a, 1992; EPA 1981; IARC 1993; Pirrone et al. 1996; Saltzman et al. 1985). Atmospheric concentrations of cadmium are generally highest in the vicinity of cadmium-emitting industries such as smelters, municipal incinerators, or fossil fuel combustion facilities (Elinder 1985a; Pirrone et al. 1996). The mean annual concentration of airborne cadmium in an area about 1 km from a zinc smelter in Colorado was 0.023 μg/m^3 ($2.3x10^{-5}$ mg/m^3) (IARC 1993). Sweet et al. (1993) conducted a study of airborne inhalable particulate matter (PM-I0) over a 2-year period in two urban/industrial areas (southeast Chicago and East St. Louis) and one rural area in Illinois. Air quality at the two urban locations is among the worst in Illinois in terms of criteria pollutants, and EPA has designated southeast Chicago as a nonattainment area. No cadmium was detected in fine particles (<2.5 μm) from the rural Illinois site (detection limit=4 ng/m^3); cadmium in coarse particles (2.5-10 μm) from this area ranged from <4 to 4.3 ng/m^3 (average <4 ng/m^3). In southeast Chicago, cadmium concentrations ranged from <4 to 9.7 ng/m^3 (average <4 ng/m^3) in fine particles and from <4 to 5.5 ng/m^3 (average <4 ng/m^3) in course particles. Cadmium concentrations in the East St. Louis area were 5-10 times higher, with a range of <4 to 115 ng/m^3 (average 15(24) ng/m^3) for fine particles and a range of <4-97 ng/m^3 (average 10(18) ng/m^3) for course particles. Annual average concentrations of atmospheric cadmium over three Great Lakes reflect the influence of industrialization and urbanization; Lake Erie's levels of 0.6 ng/m^3 were higher than fine particle concentrations of 0.2 ng/m^3 over Lake Michigan and <0.2 ng/m^3 over Lake Superior (Sweet et al. 1998). In the Lake Michigan Urban Air Toxics Study of dry deposition of metals, the flux of cadmium on the south side of Chicago was reported at about 0.01 mg/m^2 per day and levels in rural Michigan and over Lake Michigan were far lower (Holsen et al. 1993).

5.4.2 Water

Reported background levels of cadmium in unpolluted waters vary somewhat. Elinder (1992) reports that cadmium concentrations in water from the open sea range from 0.02 to 0.1 μg/L, while Eisler (1985) reports a range of 0.01-0.1 parts per billion (ppb) (μg/L). Sprague (1986) reports a cadmium concentration of 0.12 (μg/L) in deep ocean water, but adds that the concentration near the surface many decrease due to uptake of cadmium by organisms in the water. IARC (1993) reports that the concentration of cadmium dissolved in surface waters of the open ocean is <0.005 μg/L. Eisler reports that cadmium concentrations range from 0.05 to 0.2 ppb (μg/L) in fresh water and up to 0.05 in coastal seawater. Elinder (1992) reports that both fresh and coastal waters typically have cadmium concentrations less than 0.1 μg/L but that concentrations may exceed 1 μg/L in waters from areas with cadmium- and zinc-bearing mineral formations (Elinder 1992). Thornton (1992) reports that waters from the vicinity of cadmium bearing mineral deposits may have cadmium concentrations of 1,000 μg/L or more.

In a study of the water quality of the Mississippi River and its main tributaries, the U.S. Geological Survey (USGS) found cadmium concentrations ranging from 0.3 to 8 μg/L during July-August 1987; 0.05-0.9 μg/L during November-December 1987; and 0.2-6 μg/L during May-June 1988 (Taylor et al. 1990).

The cadmium concentration of natural surface water and groundwater is usually less than 1 μg/L (Elinder 1985a, 1992). Groundwater in New Jersey has an estimated median level of 1 μg Ccl/L with a high level of 405 μg/L. In a survey of groundwater surrounding waste sites, a concentration of 6,000 μg Cd/L was found (NTP 1991). The National Urban Runoff Program measured cadmium concentrations in urban storm water runoff; concentrations ranged from 0.1 to 14 μg/L in 55% of samples that were positive for cadmium (Cole et al. 1984). Cadmium in highway run-off has been detected at levels of 0.0-0.06 mg/L (0.0-60 μg/L). I n a survey of public drinking water supplies, the U.S. Public Health Service found that 4 of the 2,595 samples from 969 water systems had cadmium concentrations greater than 10 μg/L (EPA 1981). The average value was 3 μg/L. Most drinking water supplies in the United States probably do not contain more than 1 μg/L of cadmium (IARC 1993; Konz and Walker 1979), but the concentration may increase up to 10 μg/L as a result of industrial discharge or leaching from metal or plastic pipes (IARC 1993). Cadmium has been detected in water samples collected from all of the Great Lakes (IJC 1983). Cadmium has been detected in 100% of surface water and groundwater samples in a survey in New Jersey at a median concentration of 1 μg/L, and a maximum concentration of 405 μg/L (Page 1981).

5.4.3 Sediment and Soil

Cadmium concentrations in nonpolluted soil are highly variable, depending on sources of minerals and organic material. Eisler (1985) reports cadmium concentrations of 10-l,000 ppb (0.01-l ppm) in soils of nonvolcanic origin and up to 4,500 ppb (4.5 ppm) in soils of volcanic origin. Mean levels in unpolluted topsoil in the United States are approximately 0.25 ppm (EPA 1985a). Contamination of topsoil is likely the mechanism for the greatest human exposure to cadmium, mediated through uptake of soil cadmium into edible plants and tobacco (EPA 1985a). Topsoil concentrations are often more than twice as high as subsoil levels as the result of atmospheric fallout and contamination (Pierce et al. 1982). It has been reported that 90% of the cadmium in soils remains in the top 15 cm (Anonymous 1994). Markedly elevated levels may occur in topsoils near sources of contamination. For example, in the vicinity of a smelter in Helena, Montana, average soil values were 72 ppm within 1 km and 1.4 ppm between 18 and 60 km (EPA 1981). Total cadmium concentrations in soil samples taken from a SuperFund site in southeast Kansas ranged from 15 to 86 mg/kg (ppm). In the same study, soil samples were extracted with diethylenetriaminepentaacetic acid (DPTA) to approximate the plant-available metal concentrations. Extractable cadmium concentrations ranged from 0.6 to 10 mg/kg (ppm) (Abdel-Sahib et al. 1994). Soil cadmium levels in five Minnesota cities were highest in areas with the most vehicular traffic (>2 ppm in about 10% of inner-city samples) and also showed a pattern consistent with past deposition from a sewage sludge incinerator (Mielke et al. 1991). Cadmium levels up to 800 mg/kg (ppm) have been reported for soils in polluted areas (IARC 1993). Cadmium content in marine sediments ranges from 0.1 to 1.0 μg/g (ppm) in the Atlantic and Pacific oceans (Thornton 1992). Surficial sediments collected from 18 locations in three major tributaries to Newark Bay, New Jersey, had a mean cadmium concentration of 10±6 mg/kg (ppm) dry weight (Bonnevie et al. 1994). The highest cadmium concentrations were found in the Ironbound section of the Passaic River, a heavily industrialized area (29 mg/kg and 14 mg/kg), and in the Arthur Kill on the northwest side of Prall’s Island (15 mg/kg). An investigation of metals distribution in sediments along the Hudson River estuary revealed that cadmium concentrations in suspension were higher than in the bottom sediments by a factor of 30 (Gibbs 1994).

Soil samples collected from a depth of 0-15 cm along the banks of the Willamette River in Corvallis, Oregon, had a mean cadmium concentration of 1.866 mg/kg (ppm) (Nwosu et al. 1995).

Soils derived from dredged material in confined disposal facilities in the Great Lakes Region had cadmium concentrations (dry weight) of <1.9-32 ppm (Beyer and Stafford 1993). In an analytical survey of sewage

sludges from 16 large cities in the United States, cadmium concentrations ranged from 2.72 to 242 ppm (dry weight) (Gutenmann et al. 1994). The cadmium content of 242 ppm is far above the recommended concentration limit if the sludge is to be applied to agricultural land. All other sludges had cadmium contents ≤ 14.7 ppm.

Methods for decontamination of cadmium-polluted soil include leaching with acid, base, or chelating agents, and resin absorption of leachate (Urlings et al. 1988; Van Gestel et al. 1988). However, the increase in bioavailability caused by such treatment methods may result in no net decrease in cadmium content of plants grown on treated soil (Van Gestel et al. 1988).

5.4.4 Other Environmental Media

Cadmium has been detected in nearly all samples of food analyzed with sufficiently sensitive methods (Elinder 1985a). In foods obtained from unpolluted areas, the cadmium concentration is usually lower than 0.1 mg/kg fresh weight. Milk, dairy products, eggs, beef, and fish usually contain <0.01 mg/kg (ppm) while higher concentrations, 0.01-0.10 mg/kg, are typically found in vegetables, fruits, and grains (Elinder 1992). As part of the U.S. Food and Drug Administration (FDA) Total Diet Study, average concentrations of cadmium in 12 food groups were analyzed from samples collected in 27 American cities. Cadmium was found in nearly all samples, with lowest levels in beverages and fruits, and highest levels in leafy vegetables and potatoes (Gartrell et al. 1986). Table 5-2 summarizes the data from this study. Cadmium was detected in only 1 of 13,085 samples of foods collected and analyzed by 10 state food laboratories in fiscal year 1989, and the level was not considered significant (i.e., above tolerance or no tolerance set). However, no detection limit was given (Minyard and Roberts 1991). Watanabe et al. (1996) measured the cadmium content in rice samples from various areas in the world during the period from 1990 to 1995. Twenty-nine samples collected in the United States had a geometric mean of 7.43 ng Cd/g, with a standard deviation of 2.11 ng Cd/g. Shellfish, liver, and kidney meats have higher concentrations than other fish or meat (up to 1 ppm) (Elinder 1985a; IARC 1993; Schmitt and Brumbaugh 1990). Particularly high concentrations of cadmium of 2-30 mg/kg (ppm) fresh weight have been found in the edible brown meat of marine shellfish (Elinder 1992). Cadmium concentrations up to 8 μg/g in oysters and 3 μg/g in salmon flesh have been reported (IARC 1993). Sprague (1986) has reviewed tissue concentrations of cadmium for marine molluscs and crustaceans. They found that drills were higher in cadmium (average, 26 μg/g dry weight) than almost all other mollusks, although scallops and whelks also tended to be high. Clams were relatively low in cadmium (average, 0.5-l.0 μg/g dry weight). Oysters from polluted areas averaged 18 μg/g dry

Table 5-2. Cadmium Content in Selected Foods

Type of food	Average concentration (ppm)	Range of concentration (ppm)
Potatoes	0.0421	0.016–0.142
Leafy vegetables	0.0328	0.016–0.061
Grain and cereal products	0.0237	0.002–0.033
Root vegetables	0.0159	trace–0.028
Garden fruits	0.0171	trace–0.093
Oils and fats	0.0108	trace–0.033
Sugar and adjuncts	0.0109	trace–0.053
Meat, fish, and poultry	0.0057	trace–0.014
Legume vegetable	0.0044	trace–0.016
Dairy products	0.0035	trace–0.016
Fruits	0.0021	trace–0.012
Beverages	0.0013	trace
All groups		trace–0.142

Source: adapted from Gartrell et al. 1986

weight. The average concentration of cadmium in clams from polluted areas was only 2.7 μg/g dry weight, but this was significantly higher than levels in clams from clean areas. In Fiscal Year (FY) 1985/l 986, the FDA conducted a survey of cadmium, lead, and other elements in fresh clams and oysters collected from U.S. coastal areas used for shellfish production. Average cadmium levels (wet weight) were 0.09±0.06 mg/kg (ppm) (n=75) in hardshell clams, 0.05±0.04 mg/kg (n=59) in softshell clams, 0.5l±0.31 mg/kg (n=104) in Eastern oysters, and l.l±0.6 mg/kg (n=40) in Pacific oysters (Capar and Yess 1996). In FY91, FDA analyzed 5 samples of domestic clams and 24 samples of domestic oysters (collected from both coasts) for cadmium and found average concentrations of 0.06 and 0.62 mg/kg, respectively. Although no conclusions can be drawn in light of the small numbers of FY91 samples, these results to not appear to be appreciably different from those of the FY85/86 survey (Capar and Yess 1996).

Vahter et al. (1996) studied the dietary intake and uptake of cadmium in non-smoking women consuming a mixed diet low in shellfish (n=34) or with shellfish once a week or more (n=17). The shellfish diets, with a median of 22 μg Cd/day, contained twice as much cadmium as the mixed diets, which had a median of 10.5 μg Cd/day. In spite of the differences in the daily intake of cadmium, there were no statistically significant differences in the blood cadmium concentrations of the shellfish group (0.25 μg/L) and the mixed diet group (0.23 μg/L) or in the urinary cadmium concentrations of the shellfish and mixed diet groups (0.10 μg/L in both groups). These results indicate a lower absorption of cadmium in the shellfish group than in the mixed diet group or a difference in kinetics. The authors suggested that a higher gastrointestinal absorption of cadmium in the mixed diet group could be explained in part by their lower body iron stores as measured by the concentrations of serum ferritin (S-fer). A median S-fer concentration of 18 μg/L was measured for the mixed diet group compared to a median of 31 μg/L for the shellfish group.

Cadmium is accumulated mainly in the hepatopancreas (digestive gland) of the crab, and cadmium levels as high as 30-50 ppm have been detected in this edible part of the animal. Cadmium levels as high as 10 ppm also have been measured in some species of wild-growing edible mushrooms (Lind et al. 1995). Lind et al. (1995) conducted a feeding study in mice to determine the bioavailability of cadmium from crab hepatopancreas and mushroom in relation to organic cadmium. The cadmium accumulation in the liver and kidney of the mice was used as an estimate of the intestinal absorption. The group that was fed crab accumulated less cadmium in the liver and kidney than the groups fed mushrooms or inorganic cadmium salt. They concluded from the results of the study that cadmium from boiled crab has a lower bio-availability for absorption in the gastrointestinal tract of mice than inorganic cadmium and cadmium

from dried mushrooms. Almost all (99%) of the cadmium in the boiled crab hepatopancreas was associated with insoluble ligands, probably denatured protein. In fresh crab hepatopancreas, most of the cadmium is in a soluble form bound to metallothionein (Lind et al. 1995).

Significant concentrations of cadmium have been observed in fish living in stormwater ponds in Florida, especially in the redear sunfish, a bottom feeder (Campbell 1994). The mean cadmium concentration in redear sunfish living in stormwater ponds was 1.64 mg/kg wet weight compared to 0.198 mg/kg for redear sunfish living in control ponds. Similarly, the mean cadmium concentration in largemouth bass living in stormwater ponds was 3.16 mg/kg wet weight compared to 0.241 mg/kg for largemouth bass living in control ponds. Red drum, flounder, and seatrout collected from South Carolina estuaries during the period 1990-93 had consistently low cadmium levels throughout the sampling area and with respect to species (Mathews 1994). The mean concentration for all fillets and whole fish was 86.2 ppb wet weight, with 70.7% (n=164) of the samples having <25 ppb.

Cadmium concentrations of 0.5 ppm or more have been found in rice grown in cadmium-polluted areas of Japan (Nogawa et al. 1989) and China (Shiwen et al. 1990). Tobacco also concentrates cadmium from the soil, and cadmium content of cigarettes typically ranges from 1 to 2 μg/cigarette (Elinder 1985a, 1992). Some food crops, including confectionery sunflowers, have a propensity to take up cadmium from the soil in which they are grown and deposit it in the kernels. In a study to determine the cadmium burden of persons who report regular consumption of sunflower kernels, Reeves and Vanderpool (l 997) analyzed 19 different lots of sunflower kernels from the 1995 crop grown in the northern Great Plains region of North Dakota and Minnesota. They found a range of 0.33-0.67 μg Cd/g, with a mean±standard deviation of 0.48±0.11 μg/g fresh weight. The study showed that high intakes of sunflower kernels increased the intake of cadmium. However, the amount of cadmium in whole blood or in red blood cells was not affected by cadmium intake. The authors pointed out that an increased intake of sunflowers will increase not only the cadmium intake but also the intake of copper and phytate. In turn, this could reduce the availability of cadmium from this food source.

In mammals and birds, cadmium has been found in the livers and kidneys at concentrations of 0.1-2 mg/kg (ppm) and l-10 mg/kg wet weight, respectively (Elinder 1992). Animals with a long life span have very high concentrations of cadmium in their organs. Concentrations of nearly 200 mg/kg have been found in the renal cortices of old horses (Elinder 1992). Elevated cadmium levels in deer livers have prompted

several states to issue consumption advisories. Reported cadmium concentrations range from co.002 to 23 mg/kg (ppm) (dry weight) for deer livers from Connecticut, New Jersey, Illinois, and Maine, with mean concentrations of I .7, 4, 0.4, and 1.3 ppm, respectively (Musante et al. 1993).

The hepatopancreas of lobsters collected from a dredge soil dump site in Long Island Sound off New Haven, Connecticut, contained mean concentrations of 10.7 ppm cadmium in the 1970s and 8.8 ppm in 1989. Samples from another dump site off New London, Connecticut, had mean levels of 3.5 ppm in the 1970s and 3.1 ppm in 1989. Neither change in concentration with time was significant. The soft tissue of channeled whelk collected from the New Haven site contained mean cadmium concentrations of 9.3 ppm and 11.3 ppm in the 1970s and 1989, respectively. Samples from the New London site had mean cadmium concentrations of 6.0 ppm in the 1970s and 5.1 ppm in 1989. There were no statistically significant temporal changes in concentration at either site, but there were significant differences in concentrations between sites (Greig and Pereira 1993).

Eisler (1985) examined the concentrations of cadmium in a variety of aquatic and terrestrial flora and fauna and identified six trends: (1) in general, marine biota contained significantly higher cadmium residues than their freshwater or terrestrial counterparts; (2) cadmium tends to concentrate in the viscera of vertebrates, especially in the liver and kidneys; (3) cadmium concentrations are higher in older organisms than in younger ones, especially in carnivores and marine vertebrates; (4) higher concentrations for individuals of a single species collected at various locations are almost always associated with proximity to industrial/urban areas or point-source discharges of cadmium-containing wastes; (5) background levels of cadmium in crops and other plants are generally <l .0 mg/kg (ppm); and (6) cadmium concentrations in biota are dependent upon the species analyzed, the season of collection, ambient cadmium levels, and the sex of the organism.

The cadmium content of coals varies widely; concentrations of 0.01-180 μg/g (ppm) have been reported for the United States (Thornton 1992; Wilber et al. 1992).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The primary routes of human exposure to cadmium and cadmium compounds are inhalation, dermal contact, and ingestion (NTP 1991). For nonsmoking members of the general population, food is generally the greatest source of cadmium exposure. The intake of cadmium, therefore, depends upon the food items

that comprise a person's diet and may be highly variable. Sources of cadmium contamination of food by cadmium include phosphate fertilizers and sewage sludge applied to agricultural land; cadmium-plated utensils and galvanized equipment used in food processing and preparation; enamel and pottery glazes with cadmium-based pigments; and stabilizers used in food-contact plastics (Galal-Gorchev 1993). In the United States, adult intake of cadmium from food has recently been estimated to be about 30 μg/day based on the Total Diet Study, with the largest contribution from grain, cereal products, potatoes, and other vegetables (Gartrell et al. 1986). Thornton (1992) reports a typical dietary intake of 0.23 mg/week of cadmium. Somewhat lower estimates are obtained for adults using measured fecal excretion as an estimate of intake (Bunker et al. 1984; Kjellstrom et al. 1978). Assuming gastrointestinal absorption to be 5-10%, the amount of cadmium absorbed from the diet would be approximately l-3 μg/day. A decrease in soil pH due to acid precipitation may result in an increase in dietary cadmium (NTP 1991). Except in the vicinity of cadmium-emitting industries or incinerators, the intake of cadmium from drinking water or ambient air is of minor significance (Elinder 1985a). In 1988, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) established a Proposed Tolerable Weekly Intake (PTWI) of cadmium of 7 μg/kg body weight for adults as well as infants and children. JECFA also estimated the dietary intake of cadmium to be usually l-4 μg/kg body weight/week and cautioned that there is only a small safety margin between normal dietary exposure and exposure that produces adverse effects (Galal-Gorchev 1993). The WHO guideline for all forms of cadmium in drinking water is 5 μg/L (WHO 1984a). The maximal level of cadmium in drinking water and the permissible level in bottled water in the United States is 10 μg/L (IARC 1993). Near sources of cadmium pollution, individuals may inhale l-75 μg of cadmium daily. Assuming 25% absorption from the lungs, this dose of 0.25-l.9 μg of cadmium per day may contribute significantly to cadmium intake (Elinder 1985a). Cadmium accumulates mainly in the kidneys and liver, with these organs accounting for roughly 70% of the total body burden (Armstrong et al. 1992). Elinder (1992) reports an average concentration of approximately 29 ng Cd/kg wet weight for human renal cortex. IARC (1993) reports that the total body burden of nonoccupationally exposed adult subjects has been estimated to range from 9.5 to 50 mg in the United States and Europe.

It has been estimated that tobacco smokers are exposed to 1.7 μg cadmium per cigarette (NTP 1991). The amount of cadmium absorbed from smoking one pack of cigarettes per day is about l-3 μg/day (Lewis et al. 1972a; Nordberg et al. 1985), roughly the same as from the diet. This large contribution is due to the greater absorption of cadmium from the lungs than from the gastrointestinal tract (Elinder 1985a). Direct measurement of cadmium levels in body tissues confirms that smoking roughly doubles cadmium body burden in comparison to not smoking, with kidney concentrations averaging 15-20 μg/g wet weight for

nonsmokers and 30–40 µg/g wet weight for heavy smokers at the age of 50–60 (Ellis et al. 1979; Hammer et al. 1973; Lewis et al. 1972a, 1972b; NTP 1991). Ellis et al. (1979) found an increase in kidney cadmium of 0.11±0.05 mg per pack-year of smoking and an increase in liver cadmium concentration of 0.077±0.065 µg/g per pack-year. Because excretion of cadmium is very slow, half-lives of cadmium in the body are correspondingly long (17–38 years) (Wester et al. 1992).

Wester et al. (1992) investigated the percutaneous absorption of cadmium chloride from water and soil into and through human skin. They found that 116 ppb cadmium in water applied to two human cadaver skin sources at two volumes of 5 µL/cm^2 penetrated the skin to concentrations of 8.8 ±0.6% and 12.7 ±11.7% of the applied dose. The percentage doses absorbed into plasma were 0.5±0.2% and 0.6±0.6%, respectively. Cadmium in soil (13 ppb) applied to two human cadaver skin sources at doses of 0.04 g soil/cm^2 penetrated the skin at concentrations of 0.6±0.02% and 0.13±0.05%. The percentage doses absorbed into plasma were 0.01±0.01% and 0.07±0.03%. Their calculations suggest that a daily whole body exposure to cadmium at 116 ppb (as in bathing or swimming) will result in a daily systemic intake of approximately 10 µg cadmium.

Workers in a variety of occupations may be exposed to cadmium and cadmium compounds. Occupations with potential exposure to cadmium are listed below (IARC 1993). An asterisk indicates an activity with high risk because atmospheric concentrations of cadmium are high and the number of workers employed is significant.

Occupations with Potential Exposure to Cadmium and Cadmium Compounds

Alloy production*	Phosphorous production
Battery production*	Pigment production and use*
Brazing	Plastics production*
Coating	Plating
Diamond cutting	Printing
Dry color formulation	Semiconductor and superconductor production
Electroplating	Sensors production
Electrical contacts production	Smelting and refining*
Enameling	Solar cells production
Engraving	Soldering
Glasswork	Stabilizer production
Laser cutting	Textile printing
Metallizing	Thin film production
Paint production and use	Transistors production
Pesticide production and use	Welding

Highest levels of exposure would be expected to occur in operations involving heating cadmium-containing products by smelting, welding, soldering, or electroplating, and also in operations associated with producing cadmium powders (OSHA 1990). The primary route of occupational exposure is through inhalation of dust and fumes, and also incidental ingestion of dust from contaminated hands, cigarettes, or food (Adamsson et al. 1979; NTP 1991).

Concentrations of airborne cadmium found in the workplace vary considerably with the type of industry and the specific working conditions. Processes that involve high temperatures can generate cadmium oxide fumes that are absorbed very efficiently through the lungs (IARC 1993). Deposition and absorption of dust containing different compounds depend upon particle size (IARC 1993).

These exposures can be controlled through use of personal protective equipment and good industrial hygiene practices, and through operating procedures designed to reduce workplace emissions of cadmium (OSHA 1990). As an example of cadmium emissions reduction, cadmium air concentrations in the solution room of a U.S. cadmium production facility were approximately 3,000 $\mu g/m^3$ before 1955, 1,500 $\mu g/m^3$ from 1955 to 1964, and 150 $\mu g/m^3$ subsequently (IARC 1993).

Data from the National Occupational Exposure Survey (NOES), conducted by NIOSH from 1981 to 1983, estimated the number of workers potentially exposed to various chemicals in the workplace during the same period (NIOSH 1989). Data for various forms of cadmium included in the survey are summarized below:

Chemical	Number of workers potentially exposed
Cadmium sulfide	42564
Cadmium oxide	15731
Cadmium	4748
Cadmium sulfate	1313
1:1 cadmium salt of carbonic acid	164
Cadmium (form unknown)	88966
Total	153486

The NOES database does not contain information on the frequency, level, or duration of exposure of workers to any of the chemicals listed. It provides only estimates of workers potentially exposed to the chemicals.

In a 1987 report, OSHA estimated that 213,000 workers were exposed to cadmium in the workplace at levels equal to or greater than 1 μg/m^3 (NTP 1991). Of these workers, 65% were exposed to cadmium at concentrations of l-39 μg/m^3, 21% were exposed to concentrations of 40-99 μg/m^3, and 14% were exposed to concentrations greater than 100 ug/m^3. In the proposed rule for occupational exposure to cadmium, OSHA (1990) estimated that approximately 512,000 workers in the United States were exposed to cadmium, of whom approximately 70% were exposed below a time-weighted average (TWA) of 5 μg/m^3 and 81% below a TWA of 20 μg/m^3.

The OSHA final rule has established a permissible exposure limit (PEL of 5 μg/m^3 for occupational exposure to airborne cadmium (OSHA 1992). Hazardous waste workers in New Jersey have blood and urinary cadmium levels within the range of the general population and thus appear not to experience significant cadmium exposure from working at hazardous waste sites (Gochfeld et al. 1991). The American Conference of Governmental and Industrial Hygienists (ACGIH) has set their biological exposure index (BEI) at 10 μg/L (Aurelio et al. 1993).

5.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans and briefly considers potential pre-conception exposure to germ cells. Differences from adults in susceptibility to hazardous substances are discussed in Section 2.6, 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, and 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; they put things in their mouths; they may ingest inappropriate things such as dirt or paint chips; they spend more time outdoors. Children also are closer to the ground, and they do not have the judgement of adults in avoiding hazards (NRC 1993).

The placenta may act as a partial barrier to fetal exposure to cadmium. Cadmium concentration has been found to be approximately half as high in cord blood as in maternal blood in several studies including both smoking and nonsmoking women (Kuhnert et al. 1982; Lauwerys et al. 1978; Truska et al. 1989). Accumulation of cadmium in the placenta at levels about 10 times higher than maternal blood cadmium concentration has been found in studies of women in Belgium (Roels et al. 1978) and the United States (Kuhnert et al. 1982); however, in a recent study in Czechoslovakia, the concentration of cadmium in the placenta was found to be less than in either maternal or cord blood (Truska et al. 1989). Baranowska (1995) also measured the concentrations of cadmium and lead in human placenta and in maternal and neonatal (cord) blood to assess the influence of a strongly polluted environment on the content of metals in tissues and on the permeability of the placenta to cadmium and lead. Samples for the study were collected from women living in the industrial district of Upper Silesia, one of the most polluted regions in Poland. The mean (range) concentration of cadmium in the air was 11.3 (2.1-25.4) ng/m^3 (0.011 [.002-.025] μg/m^3). The mean concentrations of cadmium were 4.90 ng/mL (0.005 μg/mL) in venous blood, 0.11 μg/g in placenta, and 1.13 ng/mL (0.001 μg/mL) in cord blood. Lead concentrations were 72.50 ng/mL (.072 μg/rnL) in venous blood, 0.50 μg/g in placenta, and 38.31 ng/mL (0.038 μg/mL) in cord blood. The researcher concluded that the placenta is a better barrier for cadmium than for lead, based upon the relative decrease in metal concentrations from placenta to cord blood. The mechanism by which the placenta transports the essential metals, copper and zinc, while limiting the transport of cadmium is unknown, but may involve the approximately 1,000-fold higher concentration of zinc in the placenta and the higher affinity of cadmium than zinc for metallothionein (Goyer et al. 1992). Timing and level of cadmium exposure may influence the uptake of cadmium by the placenta, perhaps explaining the conflicting human studies. Galicia-Garcia et al. (1995) performed analyses of cadmium in maternal, cord, and newborn blood for 50 births in a Mexico City hospital. Multiple regression analyses applied to the data indicated a significant association between cord and newborn blood and between cord and maternal blood, but not among maternal and newborn blood. Birth weight of the newborns was found to be inversely associated with cord blood cadmium levels and smoking habits.

Children are most likely to be exposed to cadmium in food or water. Most ingested cadmium passes through the gastrointestinal tract without being absorbed. Only about one-twentieth of the total ingested cadmium (in food or water) is absorbed in adult humans (Ellis et al. 1979; Flanasen et al. 1978; McLellan et al. 1978; Morgan and Sherlock 1984; Newton et al. 1984; Rahola et al. 1973). The retention of cadmium in the gut slowly decreases over a period of l-3 weeks after ingestion in adults (Rahola et al. 1973). There are no data on gastrointestinal absorption of cadmium in children, although very limited

evidence exists that cadmium absorption from the gut may be greater in young animals. Oral absorption is discussed in more detail in Section 2.3.1.2. A study performed in Cincinnati, Ohio, investigated cadmium in human milk and found a mean concentration of 19 ppb (0.019 ppm) (Jensen 1983). Reported levels of cadmium in infant foods in Canada ranged from 0.00053 ppm in juices to 0.034 ppm in dry infant cereals (Debeka and McKenzie 1988). Except in the vicinity of cadmium-emitting industries or incinerators, the intake of cadmium from drinking water or ambient air is of minor significance (Elinder 1985a). Near sources of pollution, children may inhale 1-75 μg/day (Elinder 1985a). Children in the homes of parents who smoke also can be exposed to cadmium through the inhalation of environmental tobacco smoke. Although no data were found, children playing near hazardous waste sites could be exposed to cadmium in soil by hand-to-mouth activity and/or soil pica. No case studies were found on accidental poisoning of children by swallowing cadmium-containing batteries or by ingesting cadmium-containing household pesticides, which also are potential routes of exposure. No information was found concerning differences in the weight-adjusted intakes of cadmium by children.

In the Workers' Home Contamination Study conducted under the Workers' Family Protection Act (DHHS 1995), several studies were identified that reported home contamination with cadmium originating from parental occupation in a lead smelter. In a study of 396 children of ages l-9 years living less than 900 m from a primary lead smelter, 380 children (96%) had blood cadmium (CdB) levels greater than 0.0089 μg/L (Carvalho et al. 1986). The geometric mean and standard deviation were 0.087 and 2.5 μg/L, respectively. No significant relationship was found between parental occupation in the smelter and CdB in children, but a significant relationship was found between presence of smelter dross in the house and elevated CdB in children. Higher CdB was significantly associated with shorter distance from the home to the smelter. In a similar study of 263 children (ages l-9 years), living less than 900 m from a primary lead smelter, the mean cadmium in hair was significantly higher at 6.0 ppm for children whose fathers worked in lead smelters than the concentration of 3.7 ppm for children whose fathers had other jobs (Carvalho et al. 1989). In a study of 9 children from families of lead workers and 195 children (ages 4-17 years) from other families, the children from the families of lead workers had significantly higher geometric mean urinary cadmium (CdU) (0.34k2.6 μg/L) than children from other families (0.1322.2 μg/L). The CdB levels of children from families of lead workers were higher than those of the children from other families, but the difference was not statistically significant (Brockhous et al. 1988). Maravelias et al. (1989) measured the CdBs of 514 children (ages 5-12) from four schools located within various distances (500-1500 m) from a lead smelter. The average CdB was 0.36 μg/L, with a range of 0.1-3.1 μg/L.

Children from the school closest to the smelter had higher CdB levels than children from other schools, but no relationship was found between children's CdB and parental employment in the smelter.

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

The greatest potential for above-average exposure of the general population to cadmium is from smoking, which may double the exposure of a typical individual. Passive smoking does not appear to increase blood cadmium concentrations (Willers et al. 1988). Smokers with additional occupational exposure are at highest risk (Elinder 1985a). Individuals living near zinc or lead smelting operations, municipal incinerators, or other industrial processes emitting cadmium to the air will also have above-average exposure (Elinder 1985a). Exposures through inhalation are diminishing due to pollution controls at such facilities, but exposure resulting from soil contamination may continue to be significant. Persons who have corrosive drinking water and cadmium-containing plumbing, who habitually consume cadmium concentrating foods (kidney, liver, and shellfish), or who ingest grains or vegetables grown in soils treated with municipal sludge or phosphate fertilizer all may have increased exposure (Elinder 1985a). Multiple pathways of exposure may exist for populations at hazardous waste sites contaminated with cadmium (ingestion of contaminated drinking water or garden vegetables, inhalation of airborne dust, incidental ingestion of contaminated soil).

Persons who consume large quantities of sunflower kernels can be exposed to higher levels of cadmium, Reeves and Vanderpool(l 997) identified specific groups of men who were likely to consume sunflower kernels. The groups included baseball and softball players, delivery and long-distance drivers, and line workers in sunflower kernel processing plants.

Recreational and subsistence fishers that consume appreciably higher amounts of locally caught fish from contaminated waterbodies may be exposed to higher levels of cadmium associated with dietary intake (EPA 1993a). Cadmium contamination has triggered the issuance of several human health advisories. As of December 1997, cadmium was identified as the causative pollutant in five fish and shellfish consumption advisories in New York and another in New Jersey. EPA is considering including cadmium as a target analyte and has recommended that this metal be monitored in fish and shellfish tissue samples collected as part of state toxics monitoring programs. EPA recommends that residue data obtained from these monitoring programs be used by states to conduct rick assessments to determine the need for issuing fish and shellfish consumption advisories for the protection of the general public as well as recreational and

subsistence fishers Under the same program, EPA has issued a statewide advisory in Maine for cadmium in moose (EPA 1998).

5.8 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 cadmium is available. Where adequate information is not available, ATSDR, in conjunction with the 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 cadmium.

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.

5.8.1 Identification of Data Needs

Physical and Chemical Properties. The chemical and physical properties of cadmium and its salts are known well enough to permit estimation of the environmental fate of the compounds (Elinder 1985a, 1992). Additional information on properties does not appear to be crucial for evaluating potential fate.

Production, Import/Export, Use, Release, and Disposal. The production volume, producers, import/export quantities, and uses of cadmium in the United States are well documented (ABMS 1994; IARC 1993; SRI 1994; TRI961998; U.S. Bureau of Mines 1990). Production volumes have responded to demand over the past decade and there is no indication of expected significant changes (U.S. Bureau of Mines 1990). Disposal of cadmium-containing wastes is regulated by the federal government, and data are available for industrial disposal practices (EPA 1982a; HSDB 1994; U.S. Bureau of Mines 1990). Most releases of cadmium are not from production of the metal or its compounds, but from combustion or smelter emissions, land application of sewage sludge and fertilizers, and other sources; estimates of these

releases have been made (TRI961998). However, no data were located to allow estimates of the quantities of products containing cadmium that are deposited in municipal landfills. Information on current disposal practices for cadmium-containing materials would assist in evaluating potential total human exposure to cadmium.

According to the Emergency Planning and Community Right-to-Know Act of 1986,42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1996, became available in May of 1998. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate. Cadmium partitioning among media occurs, and this partitioning depends on local environmental conditions (Elinder 1985a, 1992). Cadmium may be subject to long-range transport in air and water (Keitz 1980). Cadmium is persistent in all media, although it may form organic complexes in soil and water under certain environmental conditions (Callahan et al. 1979). These processes, which are important for determining the environmental fate of cadmium, seem to be relatively well understood. Therefore, additional information on environmental fate does not appear to be essential to evaluate potential human exposure to cadmium.

Bioavailability from Environmental Media. Factors that control the bioavailability of cadmium from air, water, soil, and food have been investigated. Intestinal absorption of cadmium from food is low, about 510% (McLellan et al. 1978; Newton et al. 1984; Rahola et al. 1973), but the absorption of cadmium from soil is not known. Absorption from the lungs is somewhat greater, averaging about 25% (Nordberg et al. 1985). Estimates of dermal absorption of cadmium from soil and water on human skin have been made (Wester et al. 1992). There is some evidence that bioavailability of cadmium to plants and worms from contaminated soil is greater following remediation (Van Gestel et al. 1988). Additional information on the factors influencing bioavailability, particularly from remediated soil, are needed to assess residual risk to populations in the vicinity of reclaimed hazardous waste sites.

Food Chain Bioaccumulation. Sufficient data are available to indicate that cadmium is concentrated in plants, aquatic organisms, and animals (Alloway et al. 1990; Beyer 1986; Handy 1992a, 1992b; Kuroshima 1992; Naqui and Howell 1993; Roseman et al. 1994; Suresh et al. 1993; Vos et al. 1990). In vertebrates, cadmium accumulates in the liver and kidneys (Harrison and Klaverkamp 1990; Sileo and Beyer 1985; Vos et al. 1990). There is strong evidence for food chain bioaccumulation, but the potential for biomagnification is uncertain. Additional studies on biomagnification are needed to provide data for more accurate evaluation of the environmental impact of cadmium contamination.

Exposure Levels in Environmental Media. Extensive monitoring data are available for cadmium in all environmental media (Elinder 1985a, 1992). Cadmium has been detected in air, water, soil, plants, and food in many areas of the United States, including areas in the vicinity of hazardous waste sites (EPA 1981; IARC 1993). Estimates of human intake from these media have been made (Elinder 1985a; Gartrell et al. 1986); however, most of the data are more than 3 years old. Continuing monitoring efforts would allow more precise estimation of current sources and levels of human exposure and would assist in identifying major sources contributing to current exposure.

Reliable monitoring data for the levels of cadmium in contaminated media at hazardous waste sites are needed so that the information obtained on levels of cadmium in the environment can be used in combination with the known body burdens of cadmium to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. Cadmium has been detected in human blood, urine, breast milk, liver, kidney, and other tissues, both in occupationally exposed individuals and in the general population (Elinder 1985b; Gochfeld et al. 1991; Jensen 1983; Sikorski et al. 1989). However, few detailed current surveys of levels in U.S. populations were located; such studies are needed to establish current exposures, especially in the vicinity of hazardous waste sites. Also, more information is needed on the specific exposure levels for different cadmium salts to determine if cadmium sulfides, for example, are associated with less harmful effects than cadmium oxides (Chettle and Ellis 1992).

This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Cadmium has been measured in maternal and neonatal (cord) blood and in placenta (Baranowska 1995; Galicia-Garcia et al. 1995; Kuhnert et al. 1982; Lauwerys et al. 1978; Roels et al. 1978; Truska et al. 1989), but the resulting data are sometimes conflicting with respect to the uptake of cadmium by the placenta. Research on the effects of timing and level of exposure on cadmium uptake by the placenta might help to explain these conflicting human studies. A study performed in Cincinnati, Ohio, investigated cadmium in human milk and found a mean concentration of 19 ppb (0.019 ppm) (Jensen 1983). More recent data would be useful, both from women living in unpolluted areas (for background levels) and in polluted areas such as those near existing or former lead smelters.

Some body burden data are available for children living near lead smelters (Brockhous et al. 1988; Carvalho et al. 1986; Carvalho et al. 1989; DHHS 1995; Maravelias et al. 1989). However, none of the studies took place in the United States. Body burden data from children living in polluted and unpolluted regions (for background levels) of the United States are needed.

Current information on whether children are different in their weight-adjusted intake of cadmium via oral, inhalation, and dermal exposures was not located. A study to determine this information would be useful. Also no information was found on childhood specific means to reduce cadmium exposure.

Child health data needs relating to susceptibility are discussed in Section 2.11.2, Identification of Data Needs: Children’s Susceptibility.

Exposure Registries. The State of New York has established the Heavy Metals Registry for surveillance of occupational heavy metals absorption (Baser and Marion 1990). Health facilities, clinical laboratories, and physicians are required to report state residents with elevated levels of heavy metals, including cadmium, in blood or urine. Cadmium levels greater than 10 μg/L in blood and 5 μg/24 hours in urine were reported. Over a 5-year period, twenty-six individuals occupationally exposed to cadmium were located by this registry. Similar registries have been established in New Jersey, California, Texas, and Maryland (Baser and Marion 1990).

No other exposure registries for cadmium 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.

5.8.2 Ongoing Studies

Table 5-3 lists information located concerning ongoing research into factors controlling the potential for human exposure to cadmium.

Table 5-3. Ongoing Studies on the Potential for Human Exposure to Cadmium

Investigator	Affiliation	Research description	Sponsor
V. Baligar, C. Clark, and R.B. Ritche	Virginia Polytechnic Institute and State University, Blacksburg, VA	Uptake, transport and accumulation of trace elements, including cadmium, by plants from soil treated with coal-fired power plant by-products	USDA
E.A. Brams	Prairie View A&M University, Prairie View, TX	A quality assessment of toxic trace metals in an agricultural food chain	USDA
R.L. Chaney and R.J. Wright	Beltsville Agricultural Research Center, Beltsville, MD	Soil and plant factors affecting concentration and bioavailability of cadmium in U.S. crops	USDA
A.C. Chang, A.L. Page, and C. Amrhein	University of California, Riverside, CA	Characterization of chemistry and bioavailability of waste constituents, including cadmium, in soils	USDA
M.H. Conklin	University of Arizona, Tucson, AZ	Humic-facilitated transport of metals, including cadmium, to groundwater through the vadose zone	NIEHS
S.J. Crafts-Brandner and G. Wagner	University of Kentucky, Lexington, KY	Mechanisms of cadmium transport and sequestration in tonoplast vesicles isolated from tobacco seedlings	USDA
D.M. Ditoro	New York University Medical Center, New York, NY	Development of a model for the flux of cadmium to and from sediment	NIEHS
M.J. Gartrell	Food and Drug Administration, Washington, DC	Monitoring to determine cadmium levels in food—Total Diet Study	FDA
D.L. Grunes and W.A. Norvell	Agricultural Research Service, Ithaca, NY	Determination of soil and plant factors affecting the plant availability and translocation of potentially harmful elements, principally cadmium	USDA
H.C. Harrison	University of Wisconsin, Madison, WI	Mechanism for differences in cadmium uptake of lettuce genotypes	USDA

Table 5-3. Ongoing Studies on the Potential for Human Exposure to Cadmium (continued)

Investigator	Affiliation	Research description	Sponsor
P.A. Helmke	University of Wisconsin, Madison, WI	Ion exchange and complex ion formation affecting the solubility and plant uptake of trace metals, including cadmium; chemistry and bioavailability of waste constituents in soil.	USDA
P.A. Helmke and P. Barak	University of Wisconsin, Madison, WI	Species-specific exchange reactions controlling solubility of elements in soil and their uptake by plants	USDA
R.L. Jones	University of Illinois, Urbana, IL	Determination of total concentrations of Cu, Zn, Cd, Pb, Cr, and Ni in Illinois surface soils	USDA
L.V. Kochian	Agricultural Research Service, Ithaca, NY	Investigation and characterization of basic transport processes used by plants to absorb and translocate heavy metals, including cadmium	USDA
L.V. Kochian	Agricultural Research Service, Ithaca, NY	Identification of plant species that can be used to remediate soils polluted with heavy metals, including cadmium	USDA
A.K. Koli	South Carolina State College, Orangeburg, SC	Measurements of selected trace elements, including cadmium, in fresh fish, meats and processed meats	USDA
S. Kuo	Washington State University Puyallup Research and Extension Center, Puyallup, WA	Chemistry and bioavailability of waste constituents, including cadmium, in soils	USDA
T.J. Logan	Ohio State University, Columbus, OH	Chemistry and bioavailability of waste constituents, including cadmium, in soils	USDA
M.B. McBride	Cornell University, Ithaca, NY	Reaction and availability of toxic metals, including cadmium, in soils over the long term	USDA
L.G. Morrill	Oklahoma State University, Stillwater, OK	Factors controlling cadmium leaching and plant uptake from fly ash/soil	USDA

Table 5-3. Ongoing Studies on the Potential for Human Exposure to Cadmium (continued)

Investigator	Affiliation	Research description	Sponsor
H. Motto and J. Walworth	Rutgers University, New Brunswick, NJ	Fate of metals, including cadmium, and nutrients from land application of wastes and manure	USDA
F.M. Morel and F. Morel	Massachusetts Institute of Technology, Cambridge, MA	Role of natural chelating agents in affecting the fate and biological effects of trace metals such as cadmium in natural waters	NSF
J.W. Odom	Auburn University, Auburn, AL USA	Occurrence, accumulation and plant availability of heavy metals, including cadmium, in acid ultisols	USDA
D.R. Parker and D.E. Crowley	University of California, Riverside, Riverside, CA	Plant uptake of cadmium complexed with organic and inorganic ligands	USDA
J.H. Peverly and J.L. Hutson	Cornell University, Ithaca, NY	Fate and movement of metals, including cadmium, in representative plant/soil systems amended with sewage sludge, composts and other wastes	USDA
P.N. Pintauro	Tulane University Medical Center, New Orleans, LA	Synthesis/application of chelating agents for removal of toxic heavy metals, including cadmium, from soils and clays at superfund waste sites	NIEHS
J.R. Preer	University of the District of Columbia, Washington, DC	Fate and transport of waste constituents, including cadmium, in soil plant systems	USDA
P.G. Reeves and R. Vanderpool	Agricultural Research Service, USDA	Health effects and bioavailability of cadmium from sunflower seed kernels	USDA
C.J. Schmitt	U.S. Fish and Wildlife Service, Columbia, MO	Analysis for cadmium and other contaminants in fish and wildlife—National Contaminant Biomonitoring Program	FWS
L.M. Shuman	University of Georgia, Athens, GA	Equilibrium of metals, including cadmium, in soils and effects on water quality	USDA

Table 5-3. Ongoing Studies on the Potential for Human Exposure to Cadmium (continued)

Investigator	Affiliation	Research description	Sponsor
R.N. Singh and R.F. Keefer	West Virginia University, Morgantown, WV	Factors affecting uptake of cadmium from soil treated with waste and manure	USDA
M. Sunthankar	IonEdge Corporation, Fort Collins, CO	Investigation of environmentally safer zinc-graphite dry plating as an alternative to cadmium electroplating	EPA
R.V. Thomann	New York University Medical Center, New York, NY	Predictive models of the fate and accumulation of metals, including cadmium, in benthic aquatic animals (crab, lobster and benthic fishes)	NIEHS
S. Toon	National Renewable Energy Laboratory	Remediation of toxic metals, including cadmium, using microorganisms	USDOE
G.J. Wagner	University of Kentucky, Lexington, KY	Genetic manipulation of cadmium uptake by tobacco leaves	USDA
R.M. Welch, W.A. Norvell, and D.L. Grunes	Agricultural Research Service, Ithaca, NY	Uptake, transportation, and interactions of essential and toxic mineral elements, including cadmium	USDA
L.Y. Young	New York University Medical Center, New York, NY	Microbial mediated transformations of cadmium in the environment	NIEHS

FDA = United States Food and Drug Administration; FWS = United States Fish and Wildlife Service; NIEHS = National Institute of Environmental Health Sciences; NSF = National Science Foundation; USDA = United States Department of Agriculture; USDOE = United States Department of Energy

Source: FEDRIP 1998

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, and/or measuring, and/or monitoring cadmium, its metabolites, and other biomarkers of exposure and effect to cadmium. 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.

6.1 BIOLOGICAL SAMPLES

The most common analytical procedures for measuring cadmium concentrations in biological samples use the methods of atomic absorption spectroscopy (AAS) and atomic emission spectroscopy (AES). In AAS analysis, the sample is heated by a flame or in a furnace until the element atomizes. The ground-state atomic vapor absorbs monochromatic radiation from a source and a photoelectric detector measures the intensity of transmitted radiation (APHA 1989). In AES analysis, the emitted radiation resulting from the thermal energy from a flame or inductively coupled plasma discharge (ICP) is measured. Methods of AAS commonly used for cadmium measurement are flame atomic absorption spectroscopy (FAAS) and graphite furnace (or electrothermal) atomic absorption spectroscopy (GFAAS or ETAAS). The most common AES method used for cadmium analysis is inductively coupled plasma atomic emission spectroscopy(ICP/AES). These basic methods of analysis are well defined and generally accepted for the analysis of cadmium.

Samples are prepared for AAS and AES methods in a variety of ways. Digestion with nitric acid is most common (Roberts and Clark 1986; Sharma et al. 1982). Cadmium in blood and plasma measured by GFAAS facilitated by a wet ashing pretreatment of samples resulted in good accuracy and reproducibility. The sample detection limit using this method was 0.4 μg/L (Roberts and Clark 1986). This method was also precise and highly reproducible in determining cadmium in whole blood, urine, and hair with 99-99.4% recoveries reported (Sharma et al. 1982). The matrix may also be modified with diammonium

hydrogen phosphate or other agents such as palladium (Pd)-based modifiers (Moreira et al. 1995) to solubilize cadmium (Vinas et al. 1997). Detection limits as low as 0.1 μg/L with recoveries ranging from 93 to 111% are reported using this technique (Subramanian and Meranger 1981; Subramanian et al. 1983). If the concentration of cadmium in the dissolved sample is below the detection limit, preconcentration techniques, such as chelation and extraction, may be employed (Gross et al. 1976; Sharma et al. 1982). Since cadmium is a ubiquitous element, the risk of contamination during sampling, processing, and analysis must be minimized by strict laboratory procedures (Elinder and Lind 1985; Salmela and Vuori 1979). In one study, contamination with cadmium was found from micropipette tips; decontamination by acid washing when micro-amounts of cadmium are to be measured is recommended (Salmela and Vuori 1982).

Current analytical improvements deal primarily with the methods of sample preparation and sample introduction to the analytical systems in order to lower the detection limits or decrease sample analysis time. Various improvements in the methods of extraction, preconcentration, chelation, complexation, and sample introduction have been developed for use with biological media. Detection limits as low as 0.003 μg/L were reported (Almendro et al. 1992; Cordero et al. 1994; Jeng et al. 1994; Katskov et al. 1994; Komarek et al. 1991; Ma et al. 1994; Welz et al. 1991).

The cadmium concentration in biological samples may also be measured by a number of other methods such as radiochemical neutron activation analysis (RNAA). One RNAA procedure involving a rapid two step solvent extraction was used for determining cadmium in tissue samples (Tandon et al. 1994). Another method to determine cadmium in biological materials is based on the ion-exchange scheme developed by SAMSAHL where cadmium is trapped on an anion exchange resin. With this method, recovery of 98% and a detection limit of 4 μg/kg were reported. The accuracy of the method was estimated by three different approaches: analysis using radiotracers in inactive sample solutions; by analyzing standards, pipetted on filter paper, and processed as samples; and determination by RNAA (Woittiez and Tangonan 1992).

Cadmium concentration in tissue may be measured both *in vivo* (Ellis 1985; Scott and Chettle 1986) and in vitro (Lieberman and Kramer 1970) by neutron activation analysis (NAA). Direct *in vivo* assessment of body burden in humans focused on the measurements of cadmium in the kidney and liver by neutron activation analysis (NAA). The detection limits reported are approximately 2 mg cadmium for the total kidney and 1.5 μg/g for the liver (Ellis 1985); 1.9 mg cadmium for the kidney and 1.3 μg/g for the liver (Scott and Chettle 1986).

X-ray fluorescence is also used for *in vivo* measurement of cadmium in the kidney (Christoffersson et al. 1987; Nilsson and Skerfving 1993; Scott and Chettle 1986; Skerfving and Nilsson 1992). The *in vivo* techniques are used for clinical measurements of individuals occupationally exposed to cadmium. Additional methods applicable to the analysis of cadmium in biological media include inductively coupled plasma/mass spectrometry (ICP/MS) (Stroh 1993; Vanhoe et al. 1994) and high performance liquid chromatography (HPLC) (Chang and Robinson 1993; Steenkamp and Coetzee 1994). Electrothemal vaporization ICP/MS has been utilized for the analysis of dentin and enamel from teeth (Gliinke et al. 1996). Electrochemical methods such as adsorptive cathodic stripping voltametry (ACSV) and potentiometric stripping analysis (PSA) have been applied to hair analysis (Zhang et al. 1993), animal tissues (LaBar and Lamberts 1994), and body fluids (Ostapczuk 1993).

Table 6-1 summarizes some of the methods used for sample preparation and analysis of cadmium in biological samples.

6.2 ENVIRONMENTAL SAMPLES

Analysis for cadmium in environmental samples is usually accomplished by AAS or AES techniques, with samples prepared by digestion with nitric acid (APHA 1989; EPA 1982b, 1983a, 1983b, 1986b, 1986d, 1986e). Since cadmium in air is usually associated with particulate matter, standard methods involve collection of air samples on glass fiber or membrane filters, acid extraction of the filters, and analysis by AAS (APHA 1977; NIOSH 1984b). Adsorptive cathodic stripping voltametry (ACSV) (Nimmo and Fones 1994), differential pulse anodic stripping voltametry (DP-ASV) (Nam et al. 1994), and epithermal neutron activation analysis (NAA) (Landsberger and Wu 1993) have also been used for air analysis. Electrothermal inductively coupled plasma mass spectrometry (ETV-ICP-MS) has also been used to analyze size classified atmospheric particles for cadmium (Ltidke et al. 1997). The accuracy of the analysis of cadmium in acid digested atmospheric samples, measured by ACSV, was evaluated and compared with graphite furnace atomic absorption spectrometry (GFAAS) and inductively coupled plasma mass spectrometry (ICP-MS). The ASCV limit of detection for cadmium was 0.6 ng/mL, higher than that of GFAAS at 0.3 ng/mL but lower than that of ICP-MS for a l-minute collection period. ACSV has advantages for analysis of low concentrations of cadmium in aerosol acid digest samples (Nimmo and Fones 1994).

Table 6-1. Analytical Methods for Determining Cadmium in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood	Digestion with nitric acid; chelation with APDC and extraction with MIBK	AAS	<1 ng/mL [a]	99	Sharma et al. 1982
Blood	Modification of matrix with diammonium hydrogen phosphate/Triton X-100	AAS/graphite furnace	0.1 µg/L	100.8±4.3	Subramanian and Meranger 1981
Blood/plasma	Digestion with nitric acid; wet ashed	AAS/graphite furnace	0.4 µg/L	No data	Roberts and Clark 1986
Serum	Dilution with ammonia/Triton X-100	ICP/MS	0.01 ng/mL	No data	Stroh 1993
Tissue and blood	Microwave digestion	FAAS/flow injection system	0.15 µg/L	No data	Welz et al. 1991
Human milk	Dilution with deionized and double distilled water	AAS	<0.01 ppb [a]	No data	Schulte-Lobbert and Bohn 1977
Hair	Digestion with nitric acid	AAS	0.07 µg/g [a]	99	Sharma et al. 1982
Kidney	None (*in vivo*)	XRF	17 µg/g	No data	Christoffersson et al. 1987
Kidney/liver	Chelation and extraction with solvent	AAS/direct aspiration	0.01 ppm [a] (liver) 1.9 mg (kidney)	No data	Gross et al. 1976
Kidney/liver	None (*in vivo*)	NAA	1.3 µg/g (liver) 1.9 mg (kidney)	No data	Scott and Chettle 1986
Muscle	Wet ashed with concentrated sulfuric acid	NAA	50 ppb	50–65	Lieberman and Kramer 1970
Urine	Dilution with nitric acid	ETAAS	0.045 µg/L	97–101	Komárek et al. 1991
Urine	Modification of matrix with diammonium hydrogen phosphate/nitric acid	AAS/graphite furnace	0.09 ng/mL	92.7–111.1	Subramanian et al. 1983

Table 6-1. Analytical Methods for Determining Cadmium in Biological Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urine	Digestion with nitric acid	AAS	5.67 ng/mL[a]	99.4	Sharma et al. 1982
Biological materials	Microwave digestion followed by extraction with APTH in MIBK	ICP/AES	0.15 ng/mL	No data	Cordero et al. 1994
Biological materials	Digestion with acid	GFAAS/flow injection system	0.003 µg/L	No data	Ma et al. 1994
Biological fluids (blood, urine)	Acidification	PSA	0.001 µg/kg	No data	Ostapczuk 1993
Biological materials	Dry tissues; irradiation followed by acid digestion	RNAA	4 µg/kg	98	Woittiez et al. 1992
Teeth, dentin and enamel	Digested in nitric acid, diluted with water	ETV-ICP-MS PN-ICP-MS	No data	No data	Grünke et al. 1996
Whole blood, urine	Modified with palladium based modifier	ETAAS	0.22 µg/L	No data	Moreira et al. 1995

[a]Lowest concentration found

AAS = atomic absorption spectroscopy; APDC = ammonium pyrrolidenedithiocarbamate; APTH = 1,5-bis[-(2-pyridyl)ethylidene]thiocarbonhydride; ETAAS = electrothermal atomic absorption spectroscopy; FAAS = flame atomic absorption; GFAAS = graphite furnace atomic absorption; ICP/AES = inductively coupled plasma atomic emission spectroscopy; ICP/MS = inductively coupled plasma mass spectrometry; MIBK = methyl isobutyl ketone; NAA = neutron activation analysis; PSA = potentiometric stripping analysis; RNAA = radio chemical neutron activation analysis; XRF = X-ray fluorescence

Three methods standardized by EPA (1982b, 1983a, 1983b) are generally used for measuring concentrations of cadmium in water. The American Public Health Association (APHA) recommends similar methods for water: AAS/direct aspiration, AAS/graphite furnace technique, and inductively coupled plasma (ICP) (API-IA 1989). In addition, the APHA describes a calorimetric method using dithizone (APHA 1989). The graphite furnace AAS technique has greater sensitivity than the direct aspiration AAS and ICP techniques for cadmium. Techniques to compensate for chemical and matrix interferences in all three methods are described by APHA (1989) and EPA (1982b, 1983a, 1983b). Water analyzed by acid digestion and measured by the AAS/direct aspiration, AAS/furnace techniques or ICP/atomic emission method resulted in recoveries ranging from 90 to 110% (EPA 1982b, 1983a, 1983b). After soils and solid wastes are extracted or solubilized by acid digestion, they may be analyzed for cadmium by the same AAS methods that are used for water (EPA 1986d, 1986e). Water can also be analyzed for cadmium by NAA methods (Saleh et al. 1993), PSA methods (Ostapczuk 1993) and anodic stripping voltametry (ASV) (Daih and Huang 1992).

Sediment and soil samples have been analyzed for cadmium using the methods of laser-excited atomic fluorescence spectroscopy in a graphite furnace (LEAFS) (Zhau et al. 1998), GFAAS (Klemm and Bombach 1995), and ETAAS (Das and Chakraborty 1997). Preparation of the samples is generally accomplished by treatment with HCl and HNO_3.

The most common method for analysis of cadmium in foods is AAS (Bruhn and Franke 1976; Dabeka 1979; Muys 1984), with GFAAS (ETAAS) being one of the most common AAS methods used (Cabrera et al. 1995; Yang et al. 1995; Zhang et al. 1997). Electrothermal vaporization isotope dilution inductively coupled plasma mass spectrometry (ETV-ID-ICP-MS) has been utilized for the analysis of fish samples (Li and Jiang 1998). Radiochemical neutron activation analysis (RNAA) (Greenberg et al. 1979; Dermelj et al. 1996), differential pulse anodic stripping voltametry (ASV) (Satzger et al. 1982, 1984), and the calorimetric dithizone method (AOAC 1984) may also be employed. The AAS techniques appear to be most sensitive, with recoveries ranging from 94 to 109% (Bruhn and Franke 1976; Muys 1984). A method used to isolate cadmium by first extracting with bismuth diethyldithiocarbamate (Bi[DDC],) and then with zinc diethyldithiocarbamate ($Zn[DDC]_2$) in chloroform and then measuring by RNAA showed 94-106% recovery (Greenberg et al. 1979).

Table 6-2 summarizes some of the methods used for sample preparation and analysis of cadmium in environmental samples.

Table 6-2. Analytical Methods for Determining Cadmium in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Collection on glass fiber filter; ashed with hydrochloric and nitric acids	Method 311; AAS	0.005 µg/m^3	90	APHA 1977
Air	Collection on membrane filter; ashed with hydrochloric and nitric acids	Method 7048; AAS	0.05 µg per sample	No data	NIOSH 1984b
Air	Irradiation UF filters	Epithermal NAA	8 ng	No data	Landsberger et al. 1993
Air (aerosols)	Acid digestion with filters	ACSV	0.6 ng/mL	100	Nimmo and Fones 1994
Atmospheric particles	Direct analysis	ETV-ICP-MS	pg/m^3 range	No data	Lüdke et al.1997
Water	Digestion with nitric acid	Method 213.1; AAS/direct aspiration	0.005 mg/L	97.8 at 0.071 mg/L	EPA 1983a
Water	Digestion with nitric acid	Method 213.2; AAS/furnance technique	0.01 µg/L	96–99	EPA 1983b
Water	Digestion with nitric acid	Method 200.7; ICP/atomic emission	4 µg/L	90–110	EPA 1982b
Water	On-line preconcentration with ion exchange or sorbent extraction columns	GFAAS/flow injection system	0.8 ng/L	No data	Welz et al. 1992
Soil	Digestion with nitric acid	Method 7130; AAS/direct aspiration	0.005 mg/L	No data	EPA 1986e
Soil	Digestion with nitric acid	Method 7131; AAS/furnance technique	0.1 µg/L	No data	EPA 1986d
Soil and sediment	Ultrasonic slurry in dilute nitric acid	GFAAS	No data	100±10	Klemm and Bombach 1995
Sediment	Digestion with hydrochloric and nitric acid	LEAFS	500 fg	No data	Zhou et al. 1998

Table 6-2. Analytical Methods for Determining Cadmium in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Soil and sediment	Digestion with hydrofluoric acid and nitric acid; complexation with DDPA using on-line sorbent extraction system	GFAAS/flow injection system	0.8 µg/L	No data	Ma et al. 1994
Food	Dry ashed; oxidization with nitric acid	ASV/differential pulse	1 ng/g	99–108	Satzger et al. 1984
Food	Dry ashed; complexation with APCD; extraction with isoamyl acetate	AAS	0.1 µg/kg	97.5±2.5	Bruhn and Franke 1976
Food	Extraction with $Bi(DDC)_3$, then with $Zn(DDC)_2$ in chloroform	RNAA	0.029 µg/g [a]	94–106	Greenberg et al. 1979
Food (24 hr diet)	Microwave digestion with nitric acid and hydrogen peroxide	GFAAS	0.004 µg/g	94–101	Yang et al. 1995
Food	Dry ashed; complexation with NaDDTC; extraction with IBMK	AAS/graphite furnace	0.1 ppb [a]	94–109	Muys 1984
Food	Homogenization followed by wet ashing	GFAAS	0.01 ppb	94–108	Zhang et al. 1997
Food	Homogenization and placement in vials	NAA	No data	No data	Dermelj et al. 1996
Fruit	Homogenized fruit slurried with zirconia spheres	ETAAS	0.3 ng/g	97.7± 0.3	Cabrera et al. 1995

[a]Lowest concentration found

AAS = atomic absorption spectroscopy; ACSV = adsorptive cathodic stripping voltametry; APCD = ammonium pyrrolidino carbodithioate;ASV = anodic stripping voltametry; $Bi(DDC)_3$ = bismuth diethyldithiocarbamate; DDPA = ammonium diethyldithiophosphate; GFAAS = graphite furnace atomic absorption; IBMK = isobutyl methyl ketone; ICP = inductively coupled plasma; NAA = neutron activation analysis; NaDDTC = sodium-diethyl-dithiocarbomate; RNAA = radiochemical neutron activation analysis; $Zn(DDC)_2$ = zinc diethyldithiocarbamate; LEAFS = Laser-excited atomic fluorescence spectrometry; ETV-ICP-MS = electrothermal vaporization inductively coupled plasma mass spectrometry

6.3 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 cadmium is available. Where adequate information is not available, ATSDR, in conjunction with the 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 cadmium.

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.

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Measurements of cadmium in blood, urine, liver, hair, and kidney are all useful biological indices for human exposure to cadmium (Roels et al. 1981b; Granereo et a1.1998; Wasiak and Ciszewska 1995). Human milk, human placentas, and maternal and neonatal blood have been investigated as means to determine exposures of women and infants to cadmium (Baranowska 1995; Abadin et al. 1997). Dentin and enamel from children's teeth have also been analyzed to assess exposure (Grüke et al. 1996). Sensitive and selective methods are available for the detection and quantitation of cadmium in these biological materials (Elinder and Lind 1985; Sharma et al. 1982). Improved methods for sample preparation and *in vivo* analysis of liver and kidney content are needed to assist in monitoring environmentally exposed populations.

Sensitive methods are also available for measuring biological markers of cadmium effect, particularly urine or serum concentration of P,-microglobulin, retinol-binding protein, metallothionein, and creatinine (Kawada et al. 1990; Roels et al. 1989; Topping et al. 1986). Additional studies to establish background levels of these indicators in unexposed populations are needed to evaluate the sensitivity of these biomarkers of effect.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Cadmium is ubiquitous in the environment and does not degrade. It is found in air, water, soil, sediments, and food. Analytical methods exist for the analysis of cadmium in all of these environmental media, and these methods have the sensitivity to measure background levels and detect elevated concentrations due to anthropogenic sources such as hazardous waste sites (APHA 1989; EPA 1982b, 1983a, 1983b, 1986b, 1986d, 1986e). Additional research to reduce chemical and matrix interferences are needed to improve the speed and accuracy of the analyses.

6.3.2 Ongoing Studies

The EPA is conducting a pilot program for comprehensive monitoring of human exposure.

The National Human Exposure Assessment Study (NHEXAS) is being conducted in three regions of the United States in order to establish relationships between environmental concentrations, exposure, dose, and health response and to determine the incidence and causes of high exposures, especially for biologically susceptible persons. One of the aims of the pilot study is to test measurement methodology for a variety of pollutants, including cadmium, in food, air, and water. As an adjunct to this pilot study, the EPA and the State of Minnesota are conducting a study of children’s exposure to toxic chemicals, including cadmium.

7. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding cadmium in air, water, and other media are summarized in Table 7-1.

ATSDR has derived a chronic-duration oral MRL of 0.0002 mg/kg/day based on renal effects in humans (Nogawa et al. 1989).

The EPA classifies cadmium as a probable human carcinogen (Group B1) and has established a reference dose (RfD) of $5x10^{-4}$ mg/kg/day in water and $1x10^{-3}$ mg/kg/day in food (IRIS 1995). The reference concentration (RfC) is undergoing review by an EPA Workgroup.

Cadmium compounds are included on the list of 189 chemicals listed as hazardous air pollutants under Section 112 of the Clean Air Act as amended (U.S. Congress 1990). Cadmium also is on the list of chemicals appearing in the Emergency Planning and Community Right-To-Know Act of 1986 (EPA 1989b, 1990c). Under Title III of this statute, owners and operators of facilities that manufacture, import, process, or otherwise use the chemicals on this list of report annually their release of those chemicals to any environmental media.

OSHA requires employers of workers who are occupationally exposed to cadmium to institute engineering controls and work practices to reduce and maintain employee exposure at or below permissible exposure limits (PEL). The employer must use engineering and work practice controls, if feasible, to reduce exposure to or below an 8-hour TWA of 5 $\mu g/m^3$ (OSHA 1992). Respirators must be provided and used during the time period necessary to install or implement feasible engineering and work practice controls. The National Institute for Occupational Safety and Health recommends that exposure not exceed the lowest feasible level (NIOSH 1992).

Cadmium acetate, cadmium bromide, and cadmium chloride also are designed as hazardous substances under Section 311 of the Federal Water Pollution Control Act; any discharge of these chemicals over a specified threshold level into navigable waters is subject to reporting requirements (EPA 1978a, 1986a). Cadmium also is included on the list of 65 toxic pollutants (EPA 1979a, 1986b) subject to general pretreatment regulations for existing and new sources of pollution. Effluent discharges of cadmium from industrial sources are subject to effluent guidelines and standards in 40 CFR Part 413, 415,421,433, 435, 440,461,469, and 471. The major industrial source categories discharging cadmium include: electroplating, inorganic chemical manufacturing, nonferrous metals manufacturing, battery manufacturing,

and sewage treatment plants, among others. For these each point source categories, cadmium is generally subject to specific regulatory limits. The maximum contaminant level goal (MCLG) for cadmium in drinking water is 0.005 mg/L; the maximum contaminant level (MCL) is 0.005 mg/L (EPA 1995).

The EPA has issued one advisory for the State of New Jersey and five advisories for the State of New York restricting the consumption of cadmium-contaminated fish and shellfish (EPA 1998). The EPA has also issued an advisory restricting the consumption of moose' liver and kidneys in the State of Maine (EPA 1998). This information is current as of December 1997, based on the EPA Fish and Wildlife Advisory Database searched in October 1998 on the Internet at:

http://www.epa.gov/OST/fishadvice/

More detailed information can be obtained from the state Public Health Department or the state Department of Natural Resources. A fish or wildlife advisory will specify the bodies of water or hunting areas with restrictions. The advisory will indicate what species and size of fish or game are of concern. The advisory may completely ban consumption or recommend limiting meals of a certain fish or wildlife species to a particular frequency. For example, an advisory may recommend that a person eat a certain type of fish no more than once a month. The advisory may indicate that only certain parts of the fish or game should not be consumed and recommend preparation methods that minimize exposure. For example, the wildlife consumption advisory issued for the state of Maine is specific for moose liver and kidney (EPA 1998). Fish and wildlife advisories may also provide restrictions specifically targeting pregnant women, nursing mothers, and young children. To reduce their exposure to cadmium, state advisory recommendations for fish consumption limits (meals per week or meals per month) should be observed.

Cadmium is a hazardous waste under the Resource Conservation and Recovery Act (RCRA) under several circumstances. Regulatory limits are applicable when it is contained in sludge applied to land used for food production (EPA 1979c, 1980c). Groundwater monitoring is required at municipal solid waste landfills (EPA 1991c) and land treatment facilities (EPA 1982e). Cadmium emissions are subject to limitations for metals when burned in boilers and industrial furnaces (EPA 1991f, 1991g, 1991h, 1991i). Hazardous waste containing cadmium also must meet treatment standards prior to land disposal (EPA 1986c, 1986d, 1988c).

The FDA has promulgated an action level to regulate the amount of cadmium in pottery and hollowware (FDA 1993).

Table 7-1. Regulations and Guidelines Applicable to Cadmium

Agency	Description	Information	References
INTERNATIONAL			
IARC	Carcinogenic classification	Group 2A	WHO 1996
WHO	Chemical of Health Significance	0.003 mg/L	WHO 1996
	Provisional tolerable weekly intake	7 µg/kg	WHO 1996
NATIONAL			
Regulations:			
a. Air			
NRC	Standards for Protection Against Radiation: Appendix B - ALIs and DACs of Radionuclides for Occupational Exposure; and Effluent Concentration	Yes	10 CFR 20 NRC 1991
	Cd - 104, 107, 109, 113m, 113, 115m, 115, 117m, 117		
	Oral ALI	$2x10^{-1}$–$2x10^{-4}$ µCi	
	Inhalation ALI	$2x10^{0}$–$1x10^{-5}$ µCi	
	Inhalation DAC	$1x10^{-9}$–$2x10^{-5}$ µCi/mL	
	Effluent Concentration	$5x10^{-12}$–$2x10^{-7}$ µCi/mL	
EPA OAQPS	NESHAP - List of Pollutants and Applicability of Part 61	Yes	40 CFR 61.01 EPA 1985
	NSPS Sewage Treatment Plants - Test Methods and Procedures	Yes	40 CFR 60.154 EPA 1989a
	NESHAP - Demonstration of Early Reduction	Yes	40 CFR 63.74 EPA 1992a
	Constructed, Reconstructed, or Modified Major Sources: Short-term *de minimis* value		40 CFR 63.44 59 FR 15504
	Cadmium oxide (proposed)	$6.37x10^{-3}$ lb/hr	EPA 1994a
	Aerospace Manufacturing and Rework: Primer and Topcoat Application Operations (Proposed)	Yes	40 CFR 63 59 FR 29216 EPA 1994b
	Secondary Lead Smelters (Proposed)	Yes	40 CFR 63 59 FR 29750 EPA 1994c
OSHA	PEL TWA All cadmium compounds	5 µg/m^3	29 CFR 1910.1027(c) OSHA 1992
b. Water:			
EPA ODW	MCL	0.005 mg/L	EPA 1995
	MCLG	0.005 mg/L	EPA 1995
	Hazardous Waste Injection Restrictions	≥100 mg/L	40 CFR 148.12 EPA 1988b
EPA OWRS	Hazardous substance		
	Cadmium acetate	Yes	40 CFR 116.4
	Cadmium bromide	Yes	EPA 1978a
	Cadmium chloride	Yes	
	Reportable quantity		
	Cadmium acetate	10 pounds	
	Cadmium bromide	10 pounds	40 CFR 117.3
	Cadmium chloride	10 pounds	EPA 1986c

Table 7-1. Regulations and Guidelines Applicable to Cadmium (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
NRC	Standards for Protection Against Radiation: Appendix B -		10 CFR 20 NRC 1991
	Effluent concentrations Cd-104, 107, 109, 113m, 113, 115m, 115, 117m, 117	$4x10^{-7}$–$3x10^{-4}$ µCi/mL	
	Concentrations for Release to Sewers Cd- 104, 107,109, 113m, 113, 115m, 115, 117m, 117	$5x10^{-6}$–$3x10^{-3}$ µCi/mL	
EPA OW	NPDES - Storm Water Discharges	Yes	40 CFR 122.26 EPA 1990a
	NPDES: Appendix D - Permit Application Testing Requirements	Yes	40 CFR 122 EPA 1983d
	Form 2C - Criteria and Standards for NPDES	Yes	40 CFR 125 EPA 1984b
	Toxics Criteria for Those States Not Complying with Clean Water Act Section 303(c)(2)(B)		40 CFR 131.36 EPA 1992b
	Freshwater - max. conc.	3.9 µg/L	
	Freshwater - continuous conc.	1.1 µg/L	
	Saltwater - max. conc.	43 µg/L	
	Saltwater - continuous conc.	9.3 µg/L	
	Identification of Test Procedures	Yes	40 CFR 136 EPA 1973
	Appendix C to Part 136 - Inductively Coupled Plasma - Atomic Emission spectrometric Method for Trace Element Analysis of Water and Wastes Method 200.7	Yes	40 CFR 136 EPA 1984c
	Appendix D to Part 136 - Precision and Recovery Statements for Methods for Measuring Metals	Yes	40 CFR 136 EPA 1990b
	Criteria for Evaluation of Permit Applications for Ocean Dumping of Materials: Environmental Impact - Constituents Prohibited as Other Than Trace Contaminants	Yes	40 CFR 227.6 EPA 1977a
	Criteria for the Management of Disposal Sites for Ocean Dumping: Guidelines for Ocean Disposal Site Baseline or Trend Assessment Surveys Under Section 102 of the Act	Yes	40 CFR 228.13 EPA 1977b
	Effluent Guidelines and Standards Toxic Pollutants	Yes	40 CFR 401.15 EPA 1979b
	General Pretreatment Regulations Appendix B - 65 Toxic Pollutants	Yes	40 CFR 403 EPA 1986d
	Electroplating of Common Metals Pretreatment Standards for Existing Sources		40 CFR 413.14 EPA 1981a
	Maximum		
	Avg. daily (4 consecutive monitoring days)	1.2 mg/L 0.7	

Table 7-1. Regulations and Guidelines Applicable to Cadmium (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
	Inorganic Chemicals		40 CFR 415.642-.645
	Cadmium Pigments and Salts Production		EPA 1984d
	Pigments BPT - Max		
	- Avg. daily value (30 consecutive days)	0.078 kg/kkg of product 0.026 kk/kkg	
	Salts - BPT - Max.	4.87×10^{-5} kg/kkg	
	- Avg. daily value (30 consecutive days)	1.62×10^{-5} kg/kkg	
	Pigment and Salts - PSES - Max.	0.94 mg/L	
	-Avg. daily value (30 consecutive days)	0.28 mg/L	
	Nonferrous Metals Mfg.: Primary Electrolytic Copper Refining - Effluent Limits		40 CFR 421.52 EPA 1984e
	Max. (1 day)		
	Avg. daily value (30 consecutive days)	0.00006 k/kkg product 0.00003 k/kkg	
	Nonferrous Metals Mfg.: Primary Zinc		40 CFR 421.83-.86
	BAT Effluent Limits, NSPS, Pretreatment Std. (new and existing sources)		EPA 1984f
	Max. (1 day)		
	Max. (monthly avg.)	0–1.234 mg/kg of product 0–0.494 mg/kg of product	
	Nonferrous Metals Mfg.: Metallurgical Acid Plants		40 CFR 421.92-.96 EPA 1985c
	BPT Effluent Limits		
	Max. (1 day)	0.180 mg/kg of 1007 sulfuric acid capacity	
	Max. (monthly avg.)	0.090 mg/kg	
	BAT Effluent Limits, NSPS, Pretreatment Standards (existing and new)		
	Max. (1 day)		
	Max. (monthly avg.)	0.511 mg/kg 0.204 mg/kg	
	Nonferrous Metals Mfg.: Secondary Indium		40 CFR 421.194-.196
	NSPS, Pretreatment Std. (new and existing)		EPA 1985h
	Max. (1 day)		
	Max. (monthly avg.)	2.105–12.170 mg/kg of product 0.929–5.370 mg/kg	
	Steam Electric Power Generating: Appendix A - 126 Priority Pollutants	Yes	40 CFR 423 EPA 1982a
	Metal Finishing		40 CFR 433.13-.14
	BPT, BAT, PSES		EPA 1983e
	Max. (1 day)	0.69 mg/L	
	Max. (monthly avg.)	0.26 mg/L	40 CFR 433.15 EPA 1985g
	NSPS, PSNS		40 CFR 433.16-.17
	Max. (1 day)	0.11 mg/L	EPA 1983f
	Max. (monthly avg.)	0.07 mg/L	

Table 7-1. Regulations and Guidelines Applicable to Cadmium (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
	Oil and Gas Extraction: *Offshore* -		40 CFR 435.13 & .15
	BAT and NSPS	3 mg/kg dry wt. - Max. stock barite	EPA 1993a 40 CFR 483.16-.17 EPA 1983f
	Ore Mining and Dressing: Platinum Ores -		40 CFR 440.113
	BAT -		EPA 1982c
	Max. (I day)	0.10 mg/L	
	Avg. daily value 30 consecutive days)	0.05 mg/L	
	Ore Mining and Dressing: General Provisions	Yes	40 CFR 440.131 EPA 1982d
	Pesticide Chemicals: Metallo-Organic Pesticide Chemicals Applicability	Yes	40 CFR 455.30 EPA 1978b
	Battery Mfg.,: Cadmium		40 CFR 461.11-.12 & .14
	BPT Effluent Limits		EPA 1984g
	Max. (1 day)	0.31–758.91 mg/kg	
	max. (monthly avg.)	0.14–360.94 mg/kg	
	BAT Effluent Limits and PSES -		
	Max. (1 day)	0.05–68 mg/kg	
	Max. (monthly avg.)	0.02–30 mg/kg	
	NSPS and PSNS		40 CFR 461.13 & .15
	Max. (I day)	0.028–40 mg/kg	EPA 1984h
	Max. (monthly avg.)	0.11–16 mg/kg	
	Electrical and Electronic Components: Cathode Ray Tube - PSES, NSPS, and PSNS		40 CFR 469.34 -.36 EPA 1983g
	Max. (1 day)	0.06 mg/L	
	Max. (monthly avg.)	0.03 mg/L	
	Nonferrous Metals Forming and Metal Powders: Precious Metals	Yes	40 CFR 471.41-.45 EPA 1985h
	BPT		
	Max. (I day)	0.001–4.12 mg/off-kg	
	Max. (monthly avg.)	0.0005–1.82 mg/off-kg	
	BAT, NSPS, PSES, PSNS		
	Max. (1 day)	0.001–2.27 mg/off-kg	
	Max. (monthly avg.)	0.0005–1.0 mg/off-kg	
	Nonferrous Metals Forming and Metal Powders: Uranium Forming		40 CFR 471.71-.73 & .75 EPA 1985i
	BPT		
	Max. (1 day)	0–0.646 mg/off-kg	
	Ma x. (monthly avg.)	0.0006–0.285 mg/off-kg	
	BPT (laundry)		
	Max. (I day)	17.8 mg/employee-day	
	Max. (monthly avg.)	7.86 mg/employee day	

Table 7-1. Regulations and Guidelines Applicable to Cadmium (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
	BAT, NSPS, PSNS Max. (1 day) Max. (monthly avg.)	 0.0007–0.068 mg/off-kg 0.0003–0.027 mg/off-kg	
	BAT, NSPS, PSNS (laundry) Max. (1 day) Max. (monthly avg.)	 5.24 mg/employee-day 2.10 mg/employee-day	
	Standards for the Use or Disposal of Sewage Sludge: Land Application - Pollutant Limits	1.9–39 kg/ha	40 CFR 503.13 EPA 1993b
	Incineration - Pollutant Limits (Risk specific concentration)	0.057 $\mu g/m^3$	40 CFR 503.43 EPA 1993c
	Frequency of Monitoring Recordkeeping	Yes	40 CFR 503.46-.47 EPA 1993d
OW	Water Quality Guidance for the Great Lakes System: Proposed Guidance: Summary of Potential Concern	Yes	58 FR 20002 EPA 1993e
c. Food:			
FDA	Color additives exempt from certification Limit for cadmium (as Cd) in bronze powder, copper powder and zinc oxide	 15 ppm	21 CFR 73.1646-.1647 FDA 1977b
	Permissible level in bottled water	0.01 mg/L	21 CFR 103.35 FDA 1977c
	Food Additives permitted for Direct Addition: Cadmium level permitted in zinc methionine sulfate tablets	 0.05 ppm	21 CFR 172.399 FDA 1981
d. Other:			
EPA OPTS	Definitions	Yes	40 CFR 165.3 EPA 1974a
	Pesticides and Containers: Procedures not recommended	Yes	40 CFR 165.12 EPA 1974b
	Recommended Disposal Procedures	Yes	40 CFR 165.11 EPA 1974c
	Recommended Disposal Procedures for Pesticides Containers and Residues	Yes	40 CFR 165.14 EPA 1974d
	Nonrefillable Container Standards: Container Design and Residue Removal (Proposed)	Yes	59 FR 6712 EPA 1994d
	Refillable Container Standards: Container Design and Residue Removal (Proposed)	Yes	59 FR 6712 EPA 1994d
	Standards for Pesticide Containment Structures (Proposed)	Yes	59 FR 6712 EPA 1994d
EPA OERR	Reportable Quantity Cadmium Cadmium acetate Cadmium bromide Cadmium chloride	 10 pounds 10 pounds 10 pounds 10 pounds	40 CFR 302.4 EPA 1989b

Table 7-1. Regulations and Guidelines Applicable to Cadmium (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
	Toxic Chemical Release Reporting Rule Cadmium and Cadmium compounds	Yes	40 CFR 372.65 EPA 1990c
	Provisional Test Guidelines: Environmental Effects Guidelines	Yes	40 CFR 795.120 EPA 1987b
	Chemical Fate Testing Guidelines: Complex Formation Ability in Water	Yes	40 CFR 796.3480 EPA 1985j
	Environmental Effects Testing Guidelines: Fish Bioconcentration Test	Yes	40 CFR 797.1520 EPA 1985k
	Avian Acute Oval Toxicity Test	Yes	40 CFR 797.2175 EPA 1985l
	Criteria for Classification of Solid Waste and Disposal Facilities Practices - Appendix I - Maximum Contaminant Levels	Yes	40 CFR 257 EPA 1991a
	Application of Solid Waste to Land and Used For Production of Food Chain Crops (Interim Final)	0.5 kg/hectare, annually	40 CFR 257.3-5 EPA 1979c
EPA OSW	Criteria for Municipal Solid Waste Landfills - Design Criteria	Yes	40 CFR 258.40EPA 1991b
	Appendix I - Constituents for Detection Monitoring	Yes	40 CFR 258EPA 1991c
	Appendix II - List of Hazardous and Organic Constituents	Yes	40 CFR 258EPA 1991d
	Definition of Hazardous Waste:		40 CFR 261.3 EPA 1992c
	Toxicity Characteristic: Maximum Conc.	1.0 mg/L	40 CFR 261.24 EPA 1990d
	Appendix VII - Basis for Listing Hazardous Waste	Yes	40 CFR 261 EPA 1981c
	Appendix VIII - Hazardous Constituents Cadmium and compounds (not otherwise specified)	Yes	40 CFR 261 EPA 1988b
	Appendix IX - Wastes Excluded Under §§ 260.20 and 260.22	Yes	40 CFR 261 EPA 1984i
	Releases from SWMUs: Max. Conc. in Limits in Groundwater	0.01 mg/L	40 CFR 264.94 EPA 1982e
	Land Treatment: Food Chain Crops - Annual Application Rate	0.5 kg/ha	40 CFR 264.276(b)(1) EPA 1982f
	Appendix IX - Groundwater Monitoring List	Yes	40 CFR 264 EPA 1982g
	Land Treatment- Waste Analysis	Yes	40 CFR 265.273 EPA 1980b
	Land Treatment - Food Chain Crops - Annual Application Rate	Yes	40 CFR 265.276 EPA 1980c
	Appendix III - EPA Interim Primary Drinking Water Standards	0.01 µg/L	40 CFR 265 EPA 1980d

Table 7-1. Regulations and Guidelines Applicable to Cadmium (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
	Permit Standards for Burners	Yes	40 CFR 266.102 EPA 1991e
	Interim Status Standards for Burners	Yes	40 CFR 266.103 EPA 1991f
	Standards to Control Metals Emissions	Yes	40 CFR 266.106 EPA 1991g
	Feed Rates and Emissions Screening Limits for Carcinogenic Metals	Yes	40 CFR 266 EPA 1991h
	Appendix VII - Health-Based Limits	1 mg/L	40 CFR 266 EPA 1991i
	Appendix IX - Very Volatile Metal	Yes	40 CFR 266 EPA 1991j
	LDR - Treatment Standards Expressed as Concentrations in Waste Extract	Yes	40 CFR 268.41 EPA 1986e
	D006	1.0 mg/L (nonww)	
	F006, F007, F008, F009, F011, F012, F039, K100	0.066 mg/L (nonww)	
	K061		
	K069	0.19 mg/L (nonww) 0.14 mg/L (nonww)	
	LDR - Treatment Standards Expressed as Specified Technologies	Yes	40 CFR 268.42 EPA 1986f
	LDR - Treatment Standards Expressed as Waste Concentrations		40 CFR 268.43 EPA 1988c
	D006	1.0 mg/L (ww)	
	F039	0.2 mg/L (ww)	
	K028	6.4 mg/L (ww)	
	K061	1.61 mg/L (ww)	
	K069, K100	1.6 mg/L (ww)	
	K101, K102	0.24 mg/L (ww)	
	LDR - Variances From a Treatment Standard	Yes	40 CFR 268.44 EPA 1986g
	LDR - Alternative Treatment Standards for Nonwaste Waters	Yes	40 CFR 268.46 EPA 1992d
	LDR - Newly Identified and Listed Hazardous Waste and Hazardous Soil: Proposed Rule - Universal Treatment Standards for Metals	Yes	59 FR 48092 EPA 1993f
	EPA Administered Permit Program Part B Information Requirements for Land Treatment	Yes	40 CFR 270.20 EPA 1983h
	Permits For Boilers and Industrial Furnaces Burning Hazardous Waste	Yes	40 CFR 270.66 EPA 1991j
	Standards for Management of Used Oil: Used Oil Specifications	2 ppm max.	40 CFR 279.11 EPA 1992e
EPA OSWER	National Contingency Plan: Data Requirements	Yes	40 CFR 300.915 EPA 1990e
	Appendix C - Revised Standard Dispersant Effectiveness and Toxicity Tests	Yes	40 CFR 300 EPA 1984j

Table 7-1. Regulations and Guidelines Applicable to Cadmium (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
	Notification Requirements	Yes	40 CFR 302.6 EPA 1985m
Guidelines:			
a. Air:			
ACGIH	TWA Cadmium and compounds (as Cd) Total dust Respirable fraction	 0.01 mg/m^3 0.002 mg/m^3	ACGIH 1996
NIOSH	IDLH (as cadmium)	9 mg/m3	NIOSH 1994
	Recommended Exposure Limit Cadmium Dust and Fumes	Lowest feasible limit (0.01 mg/m^3 LOQ)	NIOSH 1992
b. Water:			
ACGIH	BEI - in urine - in blood	5 µg/g creatinine 5 µg/L	ACGIH 1996
EPA OWRS	Ambient Water Quality Criteria Ingesting Water and Organisms	10 µg/L	EPA 1985m 50 FR 30784
NAS	SNARL 7 day chronic	 0.08 mg/L 0.005 mg/L	NRC 1980
c. Other:			
ACGIH	Cancer Class	A2	ACGIH 1996
EPA	RfD (oral) Water Food	 5x10^4 mg/kg/day 1x10^3 mg/kg/day	IRIS 1996
FDA	Action Levels (in leaching solution) Flatware Small Holloware Large Holloware	 0.5 µg/mL 0.5 µg/mL 0.25 µg/mL	 CPG 7117.06 FDA 1993
NIOSH	Carcinogenic (dust and fume)	Ca	NIOSH 1992, 1994
STATE			
Regulations and Guidelines:			
a. Air:	Acceptable ambient air concentrations	1.7x10^{-1} µg/m^3	NATICH 1992
AZ	1 hour 24 hours	1.1x10^{-1} µg/m^3	
CT	Annual 8 hours	2.9x10^{-4} µg/m^3 4.0x10^{-1} µg/m^3	
FL-FTLDLE	8 hours	1x10^{-4} µg/m^3	
FL-PINELLA	8 hours 24 hours Annual	5x10^{-1} µg/m^3 1.2x10^{-1} µg/m 5.6x10^{-4} µg/m^3	
KS	Annual	5.56x10^{-4} µg/m^3	
LA	Annual	6.0x10^{-2} µg/m^3	
MA	24 hours Annual	3x10^{-3} µg/m^3 1.0x10^{-3} µg/m^3	
MI	Annual	5.6x10^{-4} µg/m^3	

Table 7-1. Regulations and Guidelines Applicable to Cadmium (continued)

Agency	Description	Information	References
STATE (cont.)			
MT	Annual	$7.0x10^{-2}$ µg/m³	
	24 hours	$3.9x10^{-1}$ µg/m³	
NC	Annual	$5.5x10^{-1}$ µg/m³	
NV	8 hours	$1.0x10^{-3}$ µg/m³	
NY	Annual	$1.67x10^{-1}$ µg/m³	
OK	24 hours	$5.0x10^{-1}$ µg/m³	
PA (Phil)	Annual	$1.2x10^{-1}$ µg/m³	
RI	Annual	$6.0x10^{-4}$ µg/m³	
SC	24 hours	$2.5x10^{-1}$ µg/m³	
SD	8 hours	$4.0x10^{-1}$ µg/m³	
TX	Annual	$1x10^{-2}$ µg/m³	
VT	Annual	$5.7x10^{-4}$ µg/m³	
VA	24 hours	$8.0x10^{-1}$ µg/m³	
WA-SWEST	Annual	$5.6x10^{-4}$ µg/m³	
Cadmium acetate			
NC	Annual	$5.5x10^{-6}$ mg/m³	
Cadmium bromide			
NC	Annual	$5.5x10^{-6}$ mg/m³	
Cadmium chloride			
FL (Tampa)	8 hours	$5.0x10^{-4}$ mg/m³	
FL-FTLDLE	8 hours	$5.0x10^{-4}$ µg/m³	
NY	Annual	$1.67x10^{-1}$ µg/m³	
b. Water:	Drinking water quality standards		
AL		10 µg/L	FSTRAC 1990
AZ	(guideline)	5 µg/L	
	(standard)	10 µg/L	
CT	8 hours	$4.0x10^{-1}$ µg/m³	
FL-FTLDLE	8 hours	$5.0x10^{-4}$ mg/m³	
FL-PINELLA	8 hours	$5.0x10^{-1}$ µg/m³	
	24 hours	$1.2x10^{-1}$ µg/m³	
FL-TAMPA	8 hours	$5.0x10^{-4}$ mg/m³	
KS	(guideline)	5 µg/L	
MA	(standard)	10 µg/L	
ME	(guideline)	5 µg/L	
MN	(guideline)	5 µg/L	
	(standard)	10 µg/L	
ND	1 hour	$5.0x10^{-4}$ mg/m³	
NV	8 hours	$1.0x10^{-3}$ mg/m³	
NY	Annual	$1.67x10^{-1}$ µg/m³	

Table 7-1. Regulations and Guidelines Applicable to Cadmium (continued)

Agency	Description	Information	References
STATE (cont.)			
RI	(guideline) (standard)	5 µg/L 10 µg/L	
SC	24 hours	$2.5x10^{-1}$ µg/m^3	
VA	24 hours	$4.2x10^{-1}$ µg/m^3	
VT	(standard)	5 µg/L	
	Water Quality Criteria: Human Health		
AK	Maximum Contaminant Level (MCL) for Inorganic Chemicals	0.01 ng	CELDs 1994
AZ	MCL for Inorganic Chemicals-Community & Non-Trans. and Non-Community	0.01 mg/L	
	MCL for Inorganic Chem-Transient Non-Comm., Private Agricultural and Semi-Private Water	0.020 mg/L	
AL	ADEM Primary Drinking Water Standards Maximum Contaminated Level for Inorganic Chem. (MCC)	0.01 mg/L	
	Human Health Criteria - Consumption of Water & Fish	10 µg/L	
	Human Health Criteria - Fish Consumption Only	Equation for calc in Resp. T (total recovery)	
AZ	Numeric Water Quality Criteria - Domestic Water Source	5 µg/L	
	Numeric Water Quality Criteria - Fish Consumption	83 µg/L T (total recoverable)	
	Numeric Water Quality Criteria - Full Body Contact	70 µg/L T (total recoverable)	
	Numeric Water Quality Criteria - Partial Body Contact	70 µg/L T (total recoverable)	
CO	Maximum Contaminant Levels for Inorganic Chem.	.010 mg/L	
CA	Maximum Contaminant Levels for Inorganic Chem.	0.10 mg/L	
	Persistent & Bioaccumulative Toxic Substances and Their Threshold Limit Conc. Values	10,000 mg/kg as Cd	
CT	Degree of Treatment - Disinfection and Chemical Treatment	0.01 mg/L	
	Degree of Treatment - Complete Treatment	0.01 mg/L	
	Maximum Permissible Level - Limits for Inorganic Chemicals	0.01 mg/L	
DE	Primary Maximum Contaminant Levels - MCL Conc. in mg/L	0.01 mg/L	
DC	Numeric Standards of Water Quality - Cd - total recoverables	0.01 mg/L	

Table 7-1. Regulations and Guidelines Applicable to Cadmium (continued)

Agency	Description	Information	References
STATE (cont.)			
	Primary Contact Recreation & Secondary Contact Recreation - Numeric Standard µg/L	0.8545 in hardness - 1.465	
FL	Maximum Contaminant Level (mg/L)	0.005 mg/L	
	Cadmium - Shall not exceed 0.8 µg/L where water hardness is 150 µg/L or less and shall not exceed 1.10 mg/L in harder waters		
	Criteria for Class II Waters - Maximum Levels	5.0 µg/L	
GA	Maximum Contaminant Level (mg/L)	0.01 mg/L	
HI	Maximum Levels of Inorganic Chemicals	0.01 mg/L NS (no std. developed)	
IA	MCL in Class B and Class C Waters Class B Class C	 0.01 mg/L 0.01 mg/L	
	MCL for Inorganic Chemicals	0.01 mg/L	
ID	Domestic Water Supplies - Maximum Allowable Conc. - Inorganic	0.01 mg/L	
IL	Chemical Constituent Level - Conc.	0.01 mg/L	EPA 1988d
	MCL for Inorganic Chemicals	0.01 mg/L	
	General Use Waters - Upper Value	0.05 mg/L	
	secondary Contam. - Upper Value	0.15 mg/L	
IN	Continuous Criterion Conc. (4-day avg.) - Point of Water Intake - Drinking Water Standards	0.01 mg/L	CELDs 1994
	MCL for Inorganic Chemicals	0.01 mg/L	
KS	MCL for Inorganic Chemicals	0.01 mg/L	
KY	MCL for Inorganic Chemicals	0.01 mg/L	
	Maximum Conc. Level - Substances Not Linked to Ca	0.01 mg/L	
	MCL for Underground Drinking Water Sources	0.01 mg/L	
	Interim Primary Drinking Water Standards	0.01 mg/L	
MA	MCL for Inorganic Chemicals	0.01 mg/L	
MD	MCL for Inorganic Chemicals	0.01 mg/L	
	Toxic Sub-Criteria for Ambient Surface Water - Drinking Water	10 µg/L	
ME	MCL for Inorganic Chemicals	0.01 mg/L	
MN	Standards for Classes A and B Standards for Class D MCL for Inorganic Chemicals	0.01 mg/L 0.01 mg/L 0.01 mg/L	

Table 7-1. Regulations and Guidelines Applicable to Cadmium (continued)

Agency	Description	Information	References
STATE (cont.)			
MO	MCL for Inorganic Chemicals	0.01 mg/L	
MS	Numeric Criteria - Human Health Organisms Only	168 µg/L	
	Numeric Criteria - Human - Water & Organisms	10 µg/L	
MT	Groundwater	10 µg/L	EPA 1988d
NC	MCL for Inorganic Chemicals	0.01 mg/L	CELDs 1994
ND	MCL for Inorganic Chemicals	0.01 mg/L	
	Standards of Water Quality for Class I	one hour total cannot exceed in µg/L the numerical value given by e(1.128 [n hardness as mg/L]-3.828) more than once every 3 years on avg.	
NE	MCL for Inorganic Chemicals	0.01 mg/L	
	Public Drinking Water Supply Numerical Criteria	0.01 mg/L	
NH	Contaminant Levels for Inorganic Chemicals & Fluoride	0.01 mg/L	
NM	MCL for Inorganic Chemicals	0.01 mg/L	
NV	All Classes - Upper Values	0.0004 mg/L	EPA 1988d
NY	For Water Classes A, A-S, AA, AA-S - Water Quality Standards - Surface & Ground (health)	10 µg/L	CELDs 1994
OH	MCL for Inorganic Chemicals	0.01 mg/L	
	Criteria for Use Designations - Human Health (30-day avg.)	10 µg/L	
OK	Maximum Allowable Levels for Inorganic Chemicals	0.005 mg/L	
	Public and Private - Upper Value	0.01 mg/L	EPA 1988d
OR	MCL for Inorganic Chemicals	0.01 mg/L	CELDs 1994
PR	Specific Stds for Toxic Sub. Coastal Estuarine Waters Surface Waters	 5.0 µg/L Conc. In µg/L - must not exceed numerical value by 3.490 to power of (0.7852 [in hardness])	
RI	MCL's for Inorganic Chemicals	0.01 mg/L	
SC	MCL's for Inorganic Chemicals	0.01 mg/L	

Table 7-1: Regulations and Guidelines Applicable to Cadmium (continued)

Agency	Description	Information	References
STATE (cont.)			
SD	MCL's for Inorganic Chemicals	0.01 mg/L	
TN	Maximum Contaminant Level	0.01 mg/L	
	National Primary Drinking Std. - MCL	0.005 mg/L	
TX	MCL's for Inorganic Chemicals	0.01 mg/L	
UT	MCL for Inorganic Chemicals	0.005 mg/L	
	Domestic Purposes-Class IA-Upper Value	0.01 mg/L	EPA 1988
	Domestic Purposes-Class IB-Upper Value	0.01 mg/L	
	Domestic Purposes-Class IC-Upper Value	0.01 mg/L	
VA	Primary Maximum Contaminant Levels	0.01 mg/L	CELDs 1994
	Surface Water Stds for Surface Public Water Supplies	0.01 mg/L	
VT	MCL's for Inorganic Chemicals	0.01 mg/L	
	Class A and B Water - Water Quality Criteria	10 mg/L	
WA	Primary Inorganic Chemical & Physical Contaminants	0.01 mg/L	
WI	Human Threshold Criteria Public Water		
	Warm water sport fish	0.01 mg/L	
	Cold water comm.	0.01 mg/L	
	Great Lakes	0.01 mg/L	
	Human Threshold for Non-Public Water		
	Warm water sport fish	0.01 mg/L	
	Cold water comm.	0.01 mg/L	
	Great Lakes	0.01 mg/L	
	MCLGs Equal to MCLs or Action Levels	0.005 mg/L	
	Maximum Inorganic Contaminant Levels	0.005 mg/L	
WV	Public Water Surface-Category A -Upper Value	Narr. (10 mg/L)	EPA 1988d
	Criteria for Cadmium - Hardness mg/L as $CaCO_3$	soluble cadmium	CELDs 1994
	0 - 35	1 µg/L	
	36 -75	2 µg/L	
	76 -150	5 µg/L	
	>150	10 µg/L	
	Water Quality Criteria: Aquatic Life		
AL	Aquatic Life		
	Marine acute	43.0 µg/L	CELDs 1994
	Marine chronic	9.3 µg/L	
	Freshwater (acute/chronic)	See text of Regs. for Equation	
AZ	Acute & Chronic Criteria for Aquatic & Wildlife		
	Cold water fishery, warm water fishery	Equation for Calculation is in Regulations - Dissolved Cadmium	
	Effluent dominated water		
	Ephemeral		
FL	Shall Not Exceed 5.0 µg/L in Marine Waters		

Table 7-1. Regulations and Guidelines Applicable to Cadmium (continued)

Agency	Description	Information	References
STATE (cont.)			
	Maximum Conc. Levels for Mixing Zone Pollutants	100 µg/L	
IA	Class B Waters - Upper Value	0.01 mg/L	EPA 1988d
	Class B Waters - 2o Upper Limit	0.0012 mg/L	
	Class C Waters - Upper Value	0.01 mg/L	
HI	Numeric Standards for Toxic Pollutants Applicable to All Waters		
	Freshwater Acute	3+ µg/L	
	Freshwater Chronic	3+ µg/L	
	Saltwater Acute	43 µg/L	
	Saltwater Chronic	9.3 µg/L	
	Fish Consumption	NS (no std developed)	
IN	Acute and Chronic Criteria for Certain Metals (Metals conc. in µg/L)		CELDS 1994
	Hazardous Values:	Acute / Chronic	
	50	2 / 0.7	
	100	4 / 1.1	
	150	6 / 1.6	
	200	9 / 2.0	
	250	11 / 2.3	
	300	14 / 2.7	
	350	16 / 3.0	
	400	19 / 3.4	
	450	21 / 3.7	
	500	24 / 4.0	
KY	Warmwater Aquat. - Upper Value	4.0 µg/L	EPA 1988d
	Warmwater Aquat. - 2° Upper Limit	12.0 µg/L	
	Chronic Criteria conc. (µg/L)	e(0.7852[in hard-3.490])	
	Acute Criteria Conc. (µg/L)	e(1.128[in hard-3.838])	
LA	Numerical Criteria for Substances - Acute Criteria for Aquatic Life		
	Fresh water	0.66, 1.13, 2.0 µg/L	CELDs 1994
	Marine water	10.00 µg/L	
MD	Toxic Sub. Criteria for Ambient Surface Waters - Aquatic Life		
	Fresh water acute	3.9 µg/L	
	Fresh water chronic	1.1 µg/L	
	Salt water acute	43 µg/L	
	Salt water chronic	9.3 µg/L	
MO	Protection of Warmwater Aquatic Life	12 µg/L	EPA 1988d
	Cold Water Sport - Upper Value	1.2 µg/L	
MS	Numeric Criteria for All Waters		
	Freshwater acute	1.8 µg/L	
	Freshwater chronic	0.66 µg/L	
	Saltwater acute	43 µg/L	
	Saltwater chronic	9.3 µg/L	

Table 7-1. Regulations and Guidelines Applicable to Cadmium (continued)

Agency	Description	Information		References
STATE (cont.)				
MT	Aquatic Life - Hardness (µg/L)	≤125	125-200	CELDs 1994
	Chronic cold water fisheries	1.2	1.5	
	Chronic lakes	10	10	
	General warm-water fishery	10	13	
	Limited warm-water fisher	13	18	
	Class III	10 µg/L		
	Aquatic Life - Acute CWF	3.9	6.2	
	Acute lakes & GWWF	33	52	
	Acute LWWF	46	72	
NC	Fresh Surface Water (WS-I) - Upper Value	0.4 µg/L		EPA 1988d
	- 2° Upper Limit	2.0 µg/L		
	Fresh Surface Water (WS-II) - Upper Value	0.4 µg/L		
	-2° Upper Limit	2.0 µg/L		
	Fresh Surface Water (WS-III) - Upper Value	0.4 µg/L		
	- 2° Upper Limit	2.0 µg/L		
	Fresh Surface Water Class B - Upper Value	0.4 µg/L		
	- 2° Upper Limit	2.0 µg/L		
	Fresh Surface Water Class C - Upper Value	0.4 µg/L		
	- 2° Upper Limit	2.0 µg/L		
	Tidal Salt Water - Class SA - Upper Value	5.0 µg/L		
	Tidal Salt Water - Class SB - Upper Value	5.0 µg/L		
	Tidal Salt Water - Class SC - Upper Value	5.0 µg/L		
ND	Class I Streams - Upper Value	0.01 mg/L		EPA 1988d
	Class IA Streams - Upper Value	0.01 mg/L		
	Class II Streams - Upper Value	0.01 mg/L		
	Class III Streams - Upper Value	0.01 mg/L		
NJ	Fresh Waters (FW2) - Upper Value	10 µg/L		
NY	For Water Class GA (health)	10 µg/L		
	For Water Classes A, A-S, AA, AA-S, B, C (aquatic)	exp.(0.7852(in[ppm hardness])3.490		
	For Water Class D (aquatic)	exp.(1.128(in[ppm hardness])3.828		
	For Water Classes SA, SB, SC, I (aquatic)	7.7 µg/L		
	For Water Class SD (aquatic)	21 µg/L		
NV	Water Quality Standards for Aquatic Use	<(1.05 [in hardness])3.73		CELDs 1994
	Water Quality Standards for Aquatic use - 24 hr. average	<(1.05[in hardness])8.53		
OH	Warm Water Habitat. - Upper Value	Narr.		EPA 1988d
	Limited Warm Water - Upper Value	Narr.		
	Exceptional - Upper Value	Narr.		
	Seasonal Salmon - Upper Value	Narr.		
	Cold Water - Upper Value	Narr.		

Table 7-1. Regulations and Guidelines Applicable to Cadmium (continued)

Agency	Description	Information	References
STATE (cont.)			
OK	Numerical Criteria for Toxic Substances (µg/L)		
	Acute	e(1.128[in hardness])–1.6774	
	Chronic	e(0.7852[in hardness]–3.828	
	Cadmium Limit for Trout Streams		
	Acute	e(1.128[in hardness])–3828	
	Chronic	*e(.7852[in* hardness])–3.490	
RI	Fresh Water - Class B - 2° Upper Limit	Narr. µg/L	EPA 1988d
	Fresh Water - Class C - 2° Upper Limit	Narr. µg/L	
	Fresh Water - Class D - 2° Upper Limit	Narr. µg/L	
	Sea Water - Class SA - Upper Value	59 µg/L	
	Sea Water Class SA - 2° Upper Value	4.5 µg/L	
	Sea Water Class SB - Upper Value	59 µg/L	
	Sea Water Class SB - 2° Upper Value	4.5 µg/L	
	Sea Water Class SC - Upper Value	59 µg/L	
	Sea Water Class SC - 2° Upper Value	4.5 µg/L	
Trust Territories	Coastal Water - Class AA - Upper Value	5 µg/L	
	Coastal Water - Class A - Upper Value	5 µg/L	
	Coastal Water - Class B - Upper Value	5 µg/L	
	Fresh Water - Class 1 - Upper Value	0.66 µg/L	
	Fresh Water - Class 2 - Upper Value	0.66 µg/L	
UT	Aquatic Class 3A - Upper Value	0.0004 mg/L	
	Aquatic - Class 3B - Upper Value	0.004 mg/L	
	Aquatic - Class 3C - Upper Value	Narr.	
	Aquatic - Class 3D - Upper Value	Narr.	
VA	Chronic Criteria for Protection of Aquatic Life		CELDs 1994
	Freshwater	e[0.7852(in hardness)]–3.490	
	Salt water total recoverable	9.3 µg/L	
VT	Water Quality Criteria for Protection - Aquatic Biota		
	Acute criteria	exp (1.128[in hardness])– 3.828	
	Chronic criteria	exp(0.7852[in hardness])–3.49	
WI	*Acute Toxicity Criteria for Sub with Toxicity* Related Water Quality at Various Hardness Levels		
	50 ppm	1.79 µg/L	
	100 ppm	3.92 µg/L	
	200 ppm	8.57 µg/L	
WV	Specific Water Quality Criteria		
	Warm water fish/small non-fishable stream	2 µg/L	EPA 1988d
	Trout waters	3 µg/L	
	Water contact recreation	2 µg/L	

Table 7-1. Regulations and Guidelines Applicable to Cadmium (continued)

Agency	Description	Information	References
STATE (cont.)			
WY	Water Quality Standards for Fish & Aquatic Life for Special A Waters	0.0004–0.015 mg/L	CELDs 1994
	Agricultural Standards		
KS	Agricultural - Upper Value Agricultural - Upper Value	0.05 mg/L 0.01 mg/L	EPA 1988d
MO	Irrigation - Upper Value	10 µg/L	
NV	Agricultural Uses - Irrigation Agricultural Uses - Watering of Livestock Propagation of Wildlife (only	0.01 mg/L 0.05 mg/L <0.05 mg/L	
OH	Agricultural - Upper Value	50 µg/L	
UT	Agricultural Uses - Class 4 - Upper Value	0.01 mg/L	
	Recreational Standards		
DC	Primary Contact Recreation & Secondary Contact Recreation - Numeric Standards, µg/L	0.8545(in hardness)–1.465	
			CELDs 1994
UT	Recreation and Class 2A - Upper Value Recreation and Class 2B - Upper Value	Narr. Narr.	
	Groundwater Quality Standards		
AL	Maximum Conc. of Constituents for Groundwater Protection	0.01 mg/L	
CO	Agricultural Standards Maximum Conc. of Constituents for Groundwater	0.01 mg/L 0.01 mg/L	
	Maximum Conc. of Constituents for Groundwater Protection	0.01 mg/L	
DE	Maximum Conc. of Constituents for Groundwater Protection	0.01 mg/L	
IL	Maximum Conc. of Constituents for Groundwater Protection	0.01 mg/L	
MA	Maximum Criteria for Class I and Class II Groundwaters	0.01 mg/L	
	Primary Effluent Limitation for Class & and Class II Groundwaters	0.01 mg/L	
	Groundwater Protection - Max. Conc.	0.01 mg/L	
MD	Maximum Conc. of Constituents for Groundwater Protection	0.02 mg/L	
MN	Maximum Conc. of Constituents for Groundwater Protection	0.01 mg/L	
MT	Groundwater	10 µg/L	

Table 7-1. Regulations and Guidelines Applicable to Cadmium (continued)

Agency	Description	Information	References
STATE (cont.)			
NC	Water Quality Standards for Class GS Waters	0.005 mg/L	
NE	Maximum Contaminant Levels for Groundwater	0.01 mg/L	
NJ	Groundwater Quality Criteria for Class GW	Natural background	
	Groundwater Quality Criteria for Class GW2 & GW3	0.01 mg/L	
	Maximum Conc. of Constituents for Groundwater Protection	0.01 mg/L	
NM	Groundwater Standards - Human Health Standards	0.01 mg/L	
NY	Groundwater Effluent Standards - Class GA	20 µg/L	
	Groundwater Monitoring for Intern - Drinking Water Standards - Hazardous Waste Facilities	0.01 mg/L	
OR	Numerical Groundwater Quality Ref. Levels	0.01 mg/L	
SC	Max. Conc. of Constituents for Groundwater Protection	0.01 mg/L	
	Interim Primary Drinking Water Standards - Groundwater Quality	0.01 mg/L	
TN	EPA Interim Primary Drinking Water Standards - Groundwater	0.01 mg/L	
	Max. Conc. of Constituents for Groundwater Protection	0.01 mg/L	
TX	Max. Conc. of Constituents for Groundwater Protection	0.01 mg/L	
	Groundwater Standards	0.0004 mg/L	
UT	Groundwater Protection	0.01 mg/L	
VA	Max. Conc. of Constituents for Groundwater Protection	0.01 mg/L	
WI	Public Health Groundwater Quality Standards		
	Enforcement Standards	0.5 mg/L	
	Preventive Activation	0.5 mg/L	
WY	Max. Contaminant Levels for Groundwaters - Underground Water		
	Domestic Class I	0.01 mg/L	
	Agricultural Class II	0.01 mg/L	
	Livestock Class III	0.01 mg/L	
	Groundwater Quality Monitoring Parameters		
	Suggested Methods		
AL		6010, 7130, 7131	
CA	Groundwater Monitoring	6010, 7130	

Table 7-1. Regulations and Guidelines Applicable to Cadmium (continued)

Agency	Description	Information	References
STATE (cont.)			
CO	Monitoring Data EPA Intern Primary Drinking Water Standards	0.01 mg/L	
	Groundwater Monitoring	6010, 7130	
IL	Groundwater Monitoring List	6010, 7130	
LA	Groundwater Monitoring List	6010, 7130	
MO	Groundwater Evaluation Parameters	µg/L	
NY	Groundwater Evaluation Parameters	6010, 7130	
OH	Groundwater Evaluation Parameters	6010, 7130	
SC	Groundwater Evaluation Parameters	6010, 7130	
VA	Groundwater Evaluation Parameters	6010, 7130	
WI	Groundwater Evaluation Parameters	6010, 7130	
c. Other			
	Hazardous Waste Constituents		
AK	In landfill, must ensure cadmium application does not exceed 0.5 lbs./acre/year, or 4.5 lbs./acre/total accumulated on the life of the facility.		
AL	Maximum Concentration of Contaminants for the Tox. Characteristics	1.0 mg/L	
	For growth of food-chain crops: If cadmium contained in waste applied → pH of waste ≥ 6.5		
AL	Annual application of cadmium must not exceed → 0.5 kg/hq		
	Cumulative application of cadmium must not exceed → 5 kg/hq		
	If waste in soil has pH≥6.5 the cumulative application of cadmium from waste must not exceed 5 kg/ha if soil cation exchange capacity (CEC) is <5 meq/100g, 10kg/ha if soil (CED) is 5-15 meq/100g, and 20 kg/ha if soil (CEC is >15 meq/100g		
	Or animal feed must be the only food chain produced, the pH of the waste and soil must be 6.5		
	Specification levels for used oil subject to regulation when burned for energy recovery	2 ppm max.	

Table 7-1. Regulations and Guidelines Applicable to Cadmium (continued)

Agency	Description	Information	References
STATE (cont.)			
AZ	Must be disposed of in sanitary landfill on site approved		
	Wastewater Sludge - Annual application of cadmium must not exceed 0.5 kg/ha or 0.45 lbs/acre		
CA	Liquid Hazardous Waste Conc. - Restricted from Land Disposal	100 mg/L	
	Cannot be land disposed of if exceeds:		
	Metal containing solid waste	1.0 mg/L	
	Non RCRA waste cat., fish ash, bottom ash	1.0 mg/L	
	Non-RCRA waste, baghouse waste for foundries	1.0 mg/L	
	Cannot be land disposed of if exceeds:		
	Auto shredder waste	1.0 mg/L	
	Hazardous waste foundry sand.	1.0 mg/L	
CO	Maximum Conc. of Contaminants for Toxicity Characteristics	1.0 mg/L	
	Food chain crops cannot be grown unless:		
	Cadmium does not exceed	0.5 kg/ha	
	Cumulative application does not exceed	5 kg/ha	
	Cumulative Cadmium Appl. - <5 maq/100q - Soil Cation Exchange - Max. Cum. Appliatia	5 kg/ha	
	Cumulative Cadmium Appl. - 5-15 meq/100q – or – Soil Cation Exchange - Max. Cum. Appliatia	10 kg/ha	
	Cumulative Cadmium Appl. - >15 neq.1000q Soil Cation Exchange - max. Cum. Appliatia	20 kg/ha	
DE	Hazardous Waste Constituent		
	Cumulative App. of Cadmium from Waste If waste and soil mix has pH of 6.5 or > cum application of cadmium from waste shall not exceed - if soil cation exchange capacity is		
	<5-15 meq./100g	5 kg/ha	
	5-15 meq/100g	10 kg/ha	
	>15 meq/100g	20 kg/ha	
	Allowable Levels of Constituents in Used Oil Burned for Energy Rec. - Allowable Levels	2 ppm max.	
FL	Compost from Solid Waste Other Than Yard Waste Must Include Cadmium mg/kg Dry Weight		
IA	Maximum Contaminant Level	15 mg/kg	
IN	Application of Waste or Sludge Containing Cadmium Must Not Exceed	0.45 lbs./acre	
	Max. Metal Addition in lb./acre When Soil Cation Exchange Capacity (meq/100g)		
	<5 meq/100g	4.5 mg/kg (5)	
	5-15 meq/100g	9 mg/kg (10)	
	>15 meq/100g	18 mg/kg (20)	

Table 7-1. Regulations and Guidelines Applicable to Cadmium (continued)

Agency	Description	Information	References
STATE (cont.)			
	Allowable Conc. for Parameters Using EP Toxicity Test		
	Type IV	0.01 mg/L	
	Type III	0.1 mg/L	
	Type II	0.23 mg/L	
	Type I	1.0 mg/L	
IL	Generic Exclusion Levels - Max. for Any Single Composite Sample	0.032 mg/L	
	Max. Conc. of Contaminants for the Toxicity Characteristics	1.0 mg/L	
KY	Maximum Concentration of Contaminants for Toxic Characteristics	1.0 mg/L	
	Maximum Concentration of Waste Permitted By Rule	30 mg/kg dry wt.	
KY	Formula for Determining the Maximum Number of Tons/Acre		
	Tons waste/acre		
	Pounds of allowable cadmium per/acre (mg of cadmium per kg in sample)		
	x0.002		
	Max. Metal Cumulative Conc. Soil Exchange Capacity (meq/100g)		
	0-5	4.46 mg/kg	
	5-15	8.92 mg/kg	
	5+	17.84 mg/kg	
LA	Max. Allowable Metal Loading (lb./acre) Soil Cation Exchange Capacity		
	<5 meq/100g	5 lb/acre	
	<5-15 meq/100g	10 lb/acre	
	>15 meq/100g	20 lb/acre	
	Maximum Conc. of Contaminants for Toxicity Characteristics	1.0 mg/L	
	Liquid Hazardous Waste - containing the following metals or cpds. of these metals at conc. greater than or equal to - cadmium		
	pH of waste and soil mixture is 6.5 or > at time of each waste application except for waste containing cadmium at conc. of 2 mg/kg dry wt or less.		
MA	Sludge Conc. - Max. Allowable Conc, in ppm Dry Wt. (Type 1 Sludge)	2 ppm	
	Sludge or Septag Shall be Classified at Type II if Containing Substance, not exceeding	22 ppm dry wt.	
	Max. Allowable Conc. shall Not Exceed - Below Limitations Where Type II or Type III sludge or septage is land applied excluding soil background level - 7 than 5	4.5 lbs/acre	
	5 or more	4.5 lbs/acre	
	Max. Conc. of Contaminants of the Toxicity Characteristics	1.0 mg/L	

Table 7-1. Regulations and Guidelines Applicable to Cadmium (continued)

Agency	Description	Information	References
STATE (cont.)			
	Liquid Hazardous Waste Containing Cadmium at Conc. Greater		
ME	Max. Permissible Conc. of Heavy Metals - for Application of Residuals and Sludges Onland	10 mg/kg dry wt.	
	Max. Loading Limits - (kg/ha) Based on Cation Exchange		
	<5 meq/100g	2.5 kg/ha	
	5-15 meq/100g	5kg/ha	
	>15 meq/100g	5 kg/ha	
	Max. Conc. of Contaminants of Toxicity Characteristics	1.0 mg/L	
MD	Max. Conc. of Contaminants of Toxicity Characteristics	1.0 mg/L	
MN	Max. Conc. of Contaminants of Toxicity Characteristics	1.0 mg/L	
MS	Max. Cum. Heavy Metal Loading Rate		
	kg/ha(CELL 5)	5 kg/ha	
	lb/acre (CELL 5)	4.4 lbs/acre	
	CEC 5-15	10 kg/ha	
	5-15	8.9 lb/acre	
	CEC >15	20 kg/ha	
	>15	17.8 lbs/acre	
MT	Max. Conc. of Contaminants of Toxicity Characteristics	1.0 mg/L	
ND	Max. Allowable Conc. of Contaminants for Characteristics of EPTOX.	1.0 mg/L	
	Max. Conc. of Constituents for Groundwater Protection	0.01 mg/L	
NE	Max. Allowable Conc. of Contaminants for Characteristics of EPTOX.	1.0 mg/L	
NH	Max. Allowable Conc. of Contaminants for Characteristics of EPTOX.	1.0 mg/L	
NJ	Maximum Conc. of Contaminants for the Toxicity Characteristics	1.0 mg/L	
NY	Max. Conc. of Contaminant for the Characteristics of EP toxicity	1.01 mg/L	
	Max. Conc. of Constituent for Groundwater Protection	0.01 mg/L	
OH	Max. Conc. of Contaminant for the Toxicity Characteristics	1.0 mg/L	
	Max. Conc. of Constituents for Groundwater Protection	0.02 mg/L	
PA	Max. Conc. of Contaminant for the Toxicity Characteristics	1.0 mg/L	
SC	Max. Conc. of Contaminant for the Toxicity Characteristics	1.0 mg/L	

Table 7-1. Regulations and Guidelines Applicable to Cadmium (continued)

Agency	Description	Information	References
STATE (cont.)			
TX	Allowable Conc. of Contaminant for the Toxicity Characteristics		
	Inland Waters of Contaminant for the Toxicity Characteristics		
	Average	0.05 mg/L	
	Composite	0.1 mg/L	
	Grab sample	0.2 mg/L	
TX	Allowable Conc. of the Metals for Discharge of Tidal Waters		
	Average	0.01 mg/L	
	Composite	0.2 mg/L	
	Grab sample	0.3 mg/L	
	Sludge Constituents Do Not Exceed	50 mg/kg	
TX	If Sludge if Stored on Site Under Semi-dry Conditions for 6 mos., sludge constituents do not exceed	25 mg/kg	
VA	Max. Conc. of Contaminant of Toxicity Characteristics	1.0 mg/L	
VT	Total Metals Conc. Standards for Waste	25 mg/kg dry wt.	
	Max. Conc. of Contaminant of Toxicity Characteristics	1.0 mg/L	
WA	EP Toxicity List - EHW Max. Conc. Extract	>100 mg/L	
	EP Toxicity List - DH Max. Conc. In Extract	>100-10,000 mg/L	
	Max. Conc. Solid Waste Management	0.01 mg/L	
WI	Max. Conc. of Contaminant for the Tox. Characteristics	1.0 mg/L	
	EPA Interim Drinking Water Standards	0.01 mg/L	
WV	Max. Conc. of Contaminant for the Toxicity Characteristics	1.0 mg/L	
WY	Max. Conc. of Contaminant for the Toxicity Characteristics	1.0 mg/L	
	Maximum Leachable Concentration		
AL	Maximum Concentration Level	0.01 mg/L	CELDs 1994
CA	Leachable Monitoring - List of Required Constituents	--	
LA	Max. Conc. of Constituents for Groundwater Protection	0.01 mg/L	
SC	MCLs	0.01 mg/L	
TX	Constituents of Concern and Max. Leachable Conc.	0.5 mg/L	
	Restricted Pesticides		
CA	Restricted-Economic Poison Containing Cadmium		CELDs 1994
CT	Registered & Prohibited	Cadmium products	

Table 7-1. Regulations and Guidelines Applicable to Cadmium (continued)

Agency	Description	Information	References
STATE (cont.)			
HI	Restricted Use Pesticides	Any conc.	
ME	Restricted Use Pesticides		
NH	Restricted Pesticides	Any conc.	
NJ	Restricted Pesticides	Any conc.	
OR	Restricted Pesticides	Any form	
PA	Restricted Pesticides		
WI	Limited Use Pesticides	Prohibited	
	Fish and Wildlife Consumption Advisories	Number of Advisories Issued for 1997	EPA 1998
		Fish / Wildlife	
ME	Statewide	1	
NJ	Statewide: coastal waters	1	
NY	Statewide: marine and freshwater	5	

[a]Standard applies to any operation or sectors for which cadmium's standard 1910.1027 is stayed or otherwise not in effect.

Group 2A = probably carcinogenic to humans
Ca = potential occupational carcinogen
A2 = Suspected Human Carcinogen

ACGIH = American Conference of Governmental Industrial Hygienists; ALI = Annual Limits on Intake; BAT = Best Available Technology; BEI = Biological Exposure Indicator; BPT = Best Practicable Technology; DAC = Derived Air Concentrations; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; IARC = International Agency for Research on Cancer; IDLH = Immediately Dangerous to Life or Health Level; LDR = Land Disposal Restrictions; MCL = Maximum Contaminant Level; MCLG = Maximum Contaminant Level Goal; NAS = National Academy of Science; NIOSH = National Institute for Occupational Safety and Health; NPDES = National Pollutant Discharge Elimination System; NRC = National Research Council; NSPS = New Source Performance Standard; OAQPS = Office of Air Quality Planning and Standards; ODW = Office of Drinking Water; OERR = Office of Emergency and Remedial Response; OPP = Office of Pesticide Products; OSHA = Occupational Safety and Health Administration; OSW = Office of Solid Waste; OTS = Office of Toxic Substances; OWRS = Office of Water Regulations and Standards; PEL = Permissible Exposure Limit; PQL = Practical Quantitation Limit; PSES = Pretreatment Standards for Existing Sources; PSNS = Pretreatment Standard for New Sources; RfD = Reference Dose; SNARL = Suggested No Adverse Reaction Level; SWMUs = Solid Waste Management Units; TLV = Threshold Limit Value; TWA = Time-Weighted Average; WHO = World Health Organization

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9. 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.

Benchmark Dose (BMD)-is 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,,, 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-is 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-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.

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.

Immunological Effects-are functional changes in the immune response.

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

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

In vivo-Occurring within the living organism.

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

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

Lethal Dose$_{LO}$ (LD_{LO})-The lowest dose of a chemical introduced by a route other than inhalation that 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 Coeffkient (K_{ow})-The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Odds Ratio-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 &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-is 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.

Physiologically Based Pharmacodynamic (PBPD) Model-is 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-is 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 $\mu g/m^3$ 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 (FUD)-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.

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 casual 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 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily Threshold Limit Value - Time Weighted Average (TLV-TWA) may not be exceeded.

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

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

Threshold Limit Value (TLV)-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 g-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. 99-4991, 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 agencywide 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, Mailstop E-29, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name(s): Cadmium
CAS number(s): 7440-43-9
Date: March 16, 1999
Profile status: Draft 2 post-public comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Key to figure: 137
Species: Human

Minimal Risk Level: 0.0002 [X] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: Nogawa K, Honda R, Kido T. et al. 1989. A dose-response analysis of cadmium in the general environment with special reference to total cadmium intake limit. Environmental Research 48:7-16.

Experimental design: Nogawa et al. (1989) investigated the dose-response for renal effects of cadmium exposure, using the average cadmium concentration in locally produced rice as the measure of cadmium intake and urinary β_2-microglobulinuria as the index of renal damage. Subjects were 1,850 (878 male and 972 female) cadmium-exposed and 294 (133 male and 161 female) nonexposed inhabitants of the Kakchashi River basin in the Ishikawa Prefecture. Mean residence time in the polluted area ranged from 1 to more than 70 years. The cadmium content of "household" (homegrown) rice was evaluated for 22 locations in the region in 1974, and cadmium intake was adjusted for proportion of commercial rice in the diet, determined by questionnaire.

Effects noted in study and corresponding doses: Abnormal urinary β_2-microglobulin concentration was defined as $\geq$1,000 µg/L or 1,000 µg/g creatinine in morning urine. The prevalence of β_2-microglobulinuria was 5.3% in control males and 3.1% in control females. A regression equation relating total cadmium intake to prevalence of β_2-microglobulinuria was derived for exposed males and females, each divided into 12 dose groups. Both regressions were highly significant (for males, $r=0.88$, $P<0.001$, for females, $r=0.81$, $p<0.01$). For both sexes, the regression equation gave a prevalence of β_2-microglobulinuria equal to controls at a total lifetime cadmium intake of 2,000 mg. This was calculated by the authors to be 110 µg/day. Using an adult body weight of 53 kg for Japanese, this corresponds to 0.0021 mg/kg/day. This can be considered the threshold for cadmium-induced β_2-microglobulinuria.

Dose endpoint used for MRL derivation: 0.0021 mg/kg/day, renal damage (proteinuria)

[X] NOAEL [ ] LOAEL

Uncertainty factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[ ] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
No

Was a conversion used for intermittent to continuous exposure?
No.

If an oral study in animals, list conversion factors used in determining human equivalent dose:
Not an oral study in animals. No conversion factor needed.

Additional studies or pertinent information that lend support to this MRL: There is a huge database supporting the kidney as the most sensitive target organ for chronic cadmium exposure. An integrated, comprehensive kinetic model has been developed to predict the concentration of cadmium in the human renal cortex as a function of cadmium intake by the inhalation and/or oral routes (Kjellstrom and Nordberg 1978). This model is based on extensive animal and human data on the toxicokinetics and toxicity of cadmium. Kjellstrom (1986a) extended the model by considering that individuals would vary in the concentration of cadmium in the renal cortex at a given intake, and that individuals would also vary in the level of cadmium causing renal damage (the "critical concentration"). Assuming a log-normal distribution of both parameters, and a critical concentrations of 180 µg/g wet weight for 10% of the population, this model predicts the percentage of a nonsmoking population with kidney cadmium level above the critical concentration to be 2.7% at 0.0014 mg/kg/day (100 µg/day with a body weight of 70 kg) and 11% at 0.0029 mg/kg/day. Comparison with the threshold derived by the Nogawa et al. (1989) study indicates that 0.0021 mg/kg/day would be about a 7% response. Thus, the Nogawa et al. (1989) study is generally consistent with the model. An uncertainty factor of 10 is used to account for human variability.

A relevant consideration is whether the proteinuria caused by cadmium exposure should be considered an adverse effect. The increased excretion of low-molecular-weight proteins *per se* probably has no adverse effect on health. On the other hand, several studies have indicated that increased excretion of calcium also occurs at approximately the same level as proteinuria, and this is definitely an adverse effect if it leads to increased calcium wasting and osteoporosis, particularly in post-menopausal women.

Buchet et al. (1990) conducted a large scale epidemiology study (called the Cadmibel study) to establish whether environmental exposure to cadmium induces renal dysfunction and to determine the critical level of the general population. A cross-sectional study was conducted from 1985 to 1989. A stratified random sample of 2,327 people was obtained from two areas with low exposure and two with high exposure. For each exposure level, one district was rural and one was urban. Subjects filled out a detailed questionnaire and provided blood and urine (spot and 24 hour) samples for analysis. Excluded from the analysis were subjects occupationally exposed to heavy metals, those under 20 or over 80 years of age, those who could provide no reliable information on smoking habits or occupational exposure to heavy metals, and those whose 24-hour urine were not considered reliable (criteria were previously published). Determinants significantly affecting the renal measurements were traced with stepwise regression. To avoid co-linearities, independent variables considered in the model were centered. A logistic model was used to study the relation between the frequency of abnormal values of the renal measurement and the internal dose of cadmium assessed by its urinary excretion. For the multiple regression and the logistic analyses, the urinary excretion of cadmium was expressed as either the total amount excreted in 24 hours or as the concentration in the 24 hour urine. Body burden of cadmium increased with age in males and females, and with increased level of smoking. In nonsmokers of all ages, women had significantly higher blood and urine cadmium levels (possibly due to higher gastrointestinal uptake). Cadmium in urine was correlated with changes in measures of proximal tubular function. Five measures of renal effects were significantly associated with 24 hour urinary cadmium excretion: urinary excretion of retinol-binding protein (RBP), N-

acetyl-β-glucosaminidase (NAG), β_2-microglobulin (B2M), aminoacids (AA), and calcium (CA). It was estimated that more than 10% of the renal measurements would be abnormal when the cadmium excretion rate exceeded 2.87 µg/24 hours for RBP, 2.74 µg/24 hours for NAG, 3.05 µg/24 hours for B2M, 4.29 µg/24 hours for AA, and 1.92 µg/24 hours for CA. Of the population tested, 184 or 10.8% had 24 hour urinary cadmium levels of more than 2 µg. The authors suggest that, for the general population, a urinary cadmium excretion of <2 µg/24 hours would result in a low risk of renal effects. This level may be lower for diabetics since cadmium body burden and diabetes had a synergistic effect on the urinary excretion of NAG and B2M. The 2 µg/24 hours urinary level for the general population is considerably below previous studies by the authors on adult workers that showed no detectable renal effects at urinary cadmium excretion of about 10 µg/24 hours. The 10 µg/24 hours level corresponded with a renal cortex concentration of 200 ppm. This finding supports the "healthy worker" effect (i.e., that risk levels based upon worker populations underestimate the risk to the general population).

On the basis of current toxicokinetic models (i.e., oral absorption rate of 5%, daily excretion rate of 0.005% of body burden, and a third of the body burden residing in the kidneys), the authors estimate that a urinary cadmium excretion of 2 µg/24 hours corresponds to a mean renal cortex concentration of about 50 ppm (wet weight). In nonsmokers, this level is reached after 50 years of an oral daily intake of about 1 µg/kg body weight. This study indicates that the critical concentration of 180 µg/g in the kinetic model (Kjellstrom 1986a) may underpredict renal damage in the general population. A LOAEL for cadmium of 1.1 µg/kg/day was derived by an independent group based on urinary calcium as the effect measure (TERA, internet communication). The agreement of the Nogawa et al. (1989) study with the Kjellstrom model could possibly be attributed to the use of a more sensitive cutoff for β_2-microglobulinuria in the Buchet et al. (1989) study (283 µg/day vs. 1,000 µg/L) and/or to the use of too high a value for absorption of cadmium from food in the Kjellstrom and Nordberg (1978) model. Since cadmium intakes were not measured in the Buchet et al. (1990) study, and urinary or renal cadmium levels were not measured in the Nogawa et al. (1989) study, it is not possible to resolve this discrepancy at this time. However, the use of the uncertainty factor of 10 is likely to account for possible increased sensitivity demonstrated by the Buchet et al. (1990) study.

Alternative methods of deriving a Minimum Risk Level based on the benchmark dose approach and pharmacokinetic modeling (Clewell et al. 1997, Crump 1995) have been investigated by the K.S. Crump Group for cadmium and the results presented in a special report prepared for ATSDR (Crump 1998). Crump (1998) used the Nogawa et al. (1989) endpoint of kidney dysfunction based upon abnormal urinary β_2-microglobulin and creatinine levels, and the percent response data was converted to quantal response rates. The quantal endpoints were then modeled using Weibull or polynomial models. Benchmark dose levels ($BMDL_{10}$s) were derived for the 95% lower bound on the estimated bench mark dose (BMD_{10}) that corresponded to a 10% extra risk. Separate BMDs were estimated for males and females using the two models (Weibull and polynomial). Cumulative exposure levels in mg/kg were converted to mg/kg/day by dividing by 70 years of environmental exposure and 365 days/year resulting in $BMDL_{10}$s of 0.00075-0.0013 mg/kg/day. Dividing by an uncertainty factor of 10 for human variability, the resulting MRLs would be 0.000075-0.00013 mg/kg/day, a factor of 1.5 to 3 times lower than the current MRL of 0.0002 mg/kg/day (Crump 1998).

A BMD could not be derived from the data of Buchet et al. (1990) because only very broadly grouped data were reported (Crump 1998). However, a modification of a pharmacokinetic model developed by Oberdorster (1990) was used to calculate the lifetime daily oral intake of cadmium that would result in a urinary excretion of 2.7 µg Cd/day. Based upon this pharmacokinetic modeling approach, and assuming a half-life of 20 years for cadmium excretion from the body, a urinary cadmium level of 2.7 µg Cd/day corresponding to a daily oral intake of 0.84 µg/kg body weight/day was derived. This estimate assumes

that all cadmium intake is via the oral route. The 0.84 µg/kg/day estimate, based upon the Buchet et al. (1990) data, represents a LOAEL (i.e., the Buchet et al. analysis is a best estimate of the critical cadmium concentration in the kidney). An uncertainty factor for interindividual variability was not considered necessary because of the large size of the population in the Buchet et al. (1990) study. Using an uncertainty factor of 3 for a minimal LOAEL an MRL of 0.0003 mg/kg/day was derived, which is a factor of 1.5 times greater than the current MRL based on the Nogawa et al. (1989) study.

Agency Contact (Chemical Manager): Jessilyn B. Taylor

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

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-1 and 2-2) 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 2-1 and Figure 2-1 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 2-1

(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 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-1) and oral (LSE Figure 2-2) 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 2-1).

(5) Species The test species, whether animal or human, are identified in this column. Section 2.5, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 2.3, "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 endpoint 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 8 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 2-1

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, 18r NOAEL is the critical endpoint for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. 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

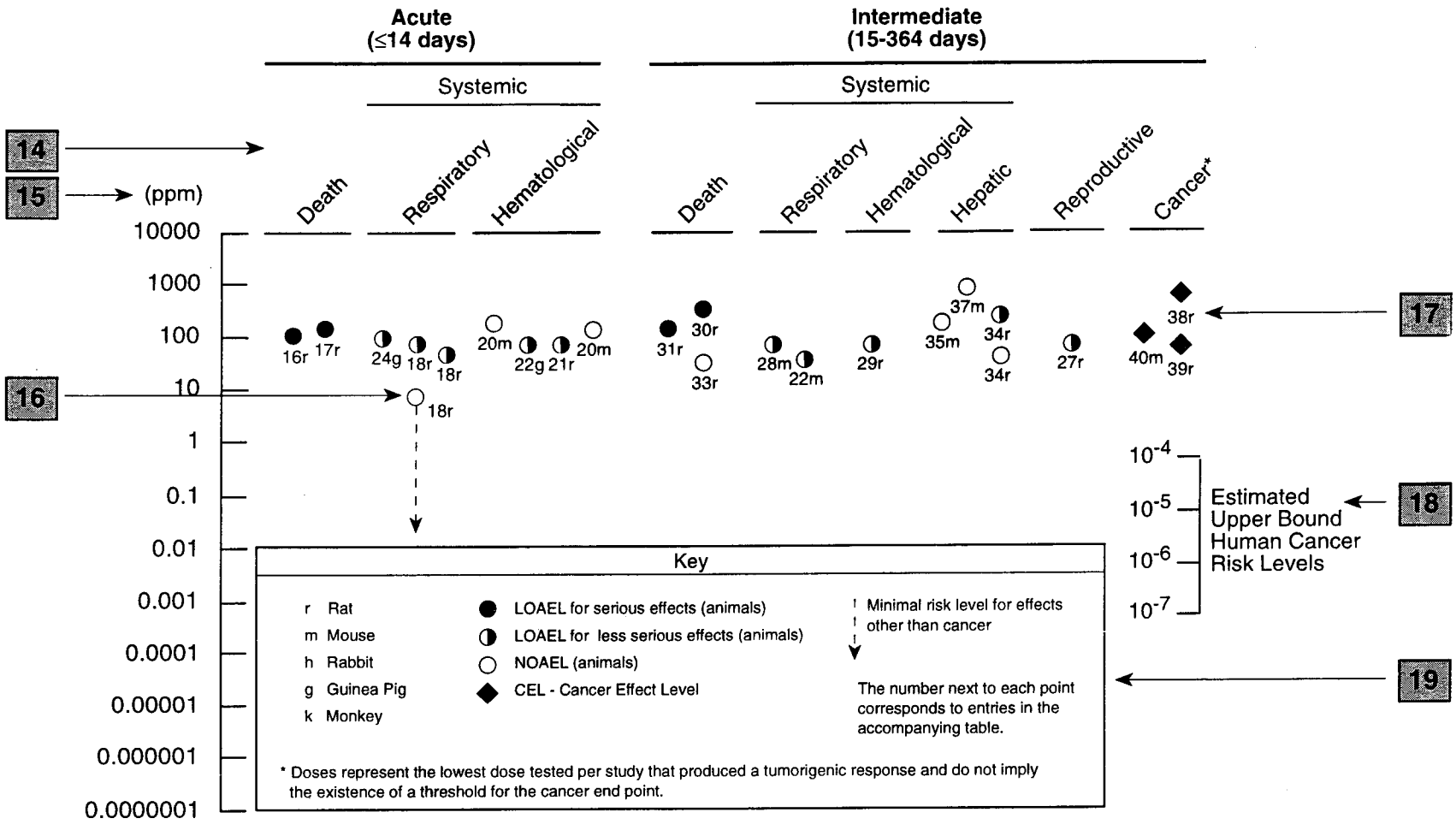
1 → **TABLE 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

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	↓	↓	↓	↓	↓		↓
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
					11		
Cancer					↓		
38	Rat	18 mo 5d/wk 7hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5d/wk 6hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5d/wk 6hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

[a] The number corresponds to entries in Figure 2-1.

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

13 → **Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation**



Chapter 2 (Section 2.5)

Relevance to Public Health

The Relevance to Public Health section 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 section 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 section. 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 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 2.5, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.8, "Interactions with Other Substances," and 2.9, "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 endpoint 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 endpoint 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.

APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADI	Acceptable Daily Intake
ADME	Absorption, Distribution, Metabolism, and Excretion
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
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
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CNS	central nervous system
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
d	day
Derm	dermal
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
ft	foot
FR	*Federal Register*
g	gram
GC	gas chromatography
Gd	gestational day
gen	generation
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
hr	hour
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
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
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

APPENDIX C

MCLG	Maximum Contaminant Level Goal
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mm Hg	millimeters of mercury
mmol	millimole
mo	month
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
NCI	National Cancer Institute
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NFPA	National Fire Protection Association
ng	nanogram
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
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
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
PID	photo ionization detector
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	Pretreatment Standards for New Sources
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
sec	second
SIC	Standard Industrial Classification
SIM	selected ion monitoring
SMCL	Secondary Maximum Contaminant Level
SMR	standard 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 Compound
TPQ	Threshold Planning Quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
VOC	Volatile Organic Compound
yr	year
WHO	World Health Organization
wk	week
>	greater than
≥	greater than or equal to
=	equal to

APPENDIX C

<	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

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