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TOXICOLOGICAL PROFILE FOR BARIUM AND BARIUM COMPOUNDS

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

August 2007

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 Barium and Barium Compounds, Draft for Public Comment was released in September 2005. This edition supersedes any previously released draft or final profile.

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

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine/Applied Toxicology Branch
1600 Clifton Road NE
Mailstop F-32
Atlanta, Georgia 30333

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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 is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

Howard Frumkin, M.D., Dr. P.H.
Director
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Agency for Toxic Substances and
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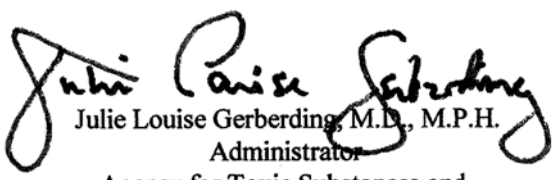

Julie Louise Gerberding, M.D., M.P.H.
Administrator
Agency for Toxic Substances and
Disease Registry

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 December 7, 2005 (70 FR 72840). For prior versions of the list of substances, see *Federal Register* notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17, 1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); February 28, 1994 (59 FR 9486); April 29, 1996 (61 FR 18744); November 17, 1997 (62 FR 61332); October 21, 1999 (64 FR 56792); October 25, 2001 (66 FR 54014); and November 7, 2003 (68 FR 63098). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

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

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

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by type of health effect (death, systemic, immunologic, reproductive), by route of exposure, and by length of exposure (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

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

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

Other Sections of Interest:

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

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY) ***Fax:*** (770) 488-4178
E-mail: cdcinfo@cdc.gov ***Internet***: http://www.atsdr.cdc.gov

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

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

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

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

Other Agencies and Organizations

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

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

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

Referrals

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

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266.

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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 Applied Toxicology Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

4. Green Border Review. Green Border review assures the consistency with ATSDR policy.

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PEER REVIEW

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

1. Michael Dourson, Ph.D., DABT, Toxicological Excellence for Risk Assessment, Cincinnati, Ohio;

2. Ernest Foulkes, Ph.D., University of Cincinnati, Cincinnati, Ohio; and

3. Richard Leggett, Ph.D., Private Consultant, Knoxville, Tennessee.

These experts collectively have knowledge of barium and barium compound'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.

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 barium and barium compounds and the effects of exposure to these chemicals.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites are then placed on the National Priorities List (NPL) and are targeted for long-term federal clean-up activities. Barium and barium compounds have been found in at least 798 of the 1,684 current or former NPL sites; however, the total number of NPL sites evaluated for these substances is not known. This information is important because these sites may be sources of exposure and exposure to this substance may harm you.

When a substance is released either from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. Such a 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 barium and barium compounds, many factors will determine whether you will be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with them. You must also consider any other chemicals you are exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT IS BARIUM?

Barium is a silvery-white metal that takes on a silver-yellow color when exposed to air. Barium occurs in nature in many different forms called compounds. These compounds are solids, existing as powders or crystals, and they do not burn well. Two forms of barium, barium sulfate and barium carbonate, are often found in nature as underground ore deposits. Barium is sometimes found naturally in drinking water and food. Because certain barium compounds (barium sulfate and barium carbonate) do not mix well with water, the amount of barium usually found in drinking water is small. Other barium compounds, such as barium chloride, barium nitrate, and barium hydroxide, are manufactured from barium sulfate. Barium compounds such

as barium acetate, barium chloride, barium hydroxide, barium nitrate, and barium sulfide dissolve more easily in water than barium sulfate and barium carbonate, but because they are not commonly found in nature, they do not typically end up in drinking water unless the water is contaminated by barium compounds that are released from waste sites.

Barium and barium compounds are used for many important purposes. Barium sulfate ore is mined and used in several industries. It is used mostly by the oil and gas industries to make drilling muds. Drilling muds make it easier to drill through rock by keeping the drill bit lubricated. Barium sulfate is also used to make paints, bricks, tiles, glass, rubber, and other barium compounds. Some barium compounds, such as barium carbonate, barium chloride, and barium hydroxide, are used to make ceramics, insect and rat poisons, and additives for oils and fuels; in the treatment of boiler water; in the production of barium greases; as a component in sealants, paper manufacturing, and sugar refining; in animal and vegetable oil refining; and in the protection of objects made of limestone from deterioration. Barium sulfate is sometimes used by doctors to perform medical tests and take x-ray photographs of the stomach and intestines.

More information on the chemical and physical properties and use of barium is found in Chapters 4 and 5.

1.2 WHAT HAPPENS TO BARIUM WHEN IT ENTERS THE ENVIRONMENT?

The length of time that barium will last in air, land, water, or sediments following release of barium into these media depends on the form of barium released. Barium compounds that do not dissolve well in water, such as barium sulfate and barium carbonate, can persist for a long time in the environment. Barium compounds, such as barium chloride, barium nitrate, or barium hydroxide, that dissolve easily in water usually do not last in these forms for a long time in the environment. The barium in these compounds that is dissolved in water quickly combines with sulfate or carbonate that are naturally found in water and become the longer lasting forms (barium sulfate and barium carbonate). Barium sulfate and barium carbonate are the barium compounds most commonly found in the soil and water. If barium sulfate and barium carbonate

are released onto land, they will combine with particles of soil. More information on the environmental fate of barium is found in Chapter 6.

1.3 HOW MIGHT I BE EXPOSED TO BARIUM?

Background levels of barium in the environment are very low. The air that most people breathe contains about 0.0015 parts of barium per billion parts of air (ppb). The air around factories that release barium compounds into the air has about 0.33 ppb or less of barium. Most surface water and public water supplies contain on average 0.030 parts of barium per million parts of water (ppm) or less, but can average as high as 0.30 ppm in some regions of the United States. In some areas that have underground water wells, drinking water may contain more barium than the 2 ppm limit set by EPA. The highest amount measured from these water wells has been 10 ppm. The amount of barium found in soil ranges from about 15 to 3,500 ppm. Some foods, such as Brazil nuts, seaweed, fish, and certain plants, may contain high amounts of barium. The amount of barium found in food and water usually is not high enough to be a health concern. However, information is still being collected to determine if long-term exposure to low levels of barium causes any health problems.

People with the greatest known risk of exposure to high levels of barium are those working in industries that make or use barium compounds. Most of these exposed persons breathe air that contains barium sulfate or barium carbonate. Sometimes they are exposed to one of the more harmful barium compounds (for example, barium chloride or barium hydroxide) by breathing the dust from these compounds or by getting them on their skin. Barium carbonate can be harmful if accidentally eaten because it will dissolve in the acids within the stomach unlike barium sulfate, which will not dissolve in the stomach. Many hazardous waste sites contain barium compounds, and these sites may be a source of exposure for people living and working near them. Exposure near hazardous waste sites may occur by breathing dust, eating soil or plants, or drinking water that is polluted with barium. People near these sites may also get soil or water that contains barium on their skin. More information on how you might be exposed to barium is found in Chapter 6.

1.4 HOW CAN BARIUM ENTER AND LEAVE MY BODY?

Barium enters your body when you breathe air, eat food, or drink water containing barium. It may also enter your body to a small extent when you have direct skin contact with barium compounds. The amount of barium that enters the bloodstream after you breathe, eat, or drink it depends on the barium compound. Some barium compounds that are soluble, such as barium chloride, can enter bloodstream more easily than insoluble barium compounds such as barium sulfate. Some barium compounds (for example, barium chloride) can enter your body through your skin, but this is very rare and usually occurs in industrial accidents at factories where they make or use barium compounds. Barium at hazardous waste sites may enter your body if you breathe dust, eat soil or plants, or drink water polluted with barium from this area.

Barium that enters your body by breathing, eating, or drinking is removed mainly in feces and urine. Most of the barium that enters your body is removed within 1–2 weeks. Most of the small amount of barium that stays in your body goes into the bones and teeth. More information on how barium enters and leaves your body is found in Chapter 3.

1.5 HOW CAN BARIUM AFFECT MY HEALTH?

Scientists use many tests to protect the public from harmful effects of toxic chemicals and to find ways for treating persons who have been harmed.

One way to learn whether a chemical will harm people is to determine how the body absorbs, uses, and releases the chemical. For some chemicals, animal testing may be necessary. Animal testing may also help identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method for getting information needed to make wise decisions that protect public health. Scientists have the responsibility to treat research animals with care and compassion. Scientists must comply with strict animal care guidelines because laws today protect the welfare of research animals.

The health effects associated with exposure to different barium compounds depend on how well the specific barium compound dissolves in water or in the stomach. For example, barium sulfate

does not easily dissolve in water and causes few harmful health effects. Doctors sometimes give barium sulfate orally or by placing it directly in the rectum of patients for purposes of making x-rays of the stomach or intestines. The use of this particular barium compound in this type of medical test is not harmful to people. Barium compounds such as barium acetate, barium chloride, barium hydroxide, barium nitrate, and barium sulfide that dissolve in water can cause harmful health effects. Barium carbonate does not dissolve in water, but does dissolve in the stomach; it can also cause harmful health effects.

Eating or drinking very large amounts of barium compounds that dissolve in water or in the stomach can cause changes in heart rhythm or paralysis in humans. Some people who did not seek medical treatment soon after eating or drinking a very large amount of barium have died. Some people who eat or drink somewhat smaller amounts of barium for a short period may experience vomiting, abdominal cramps, diarrhea, difficulties in breathing, increased or decreased blood pressure, numbness around the face, and muscle weakness. One study showed that people who drank water containing as much as 10 ppm of barium for 4 weeks did not have increased blood pressure or abnormal heart rhythms. The health effects of barium have been studied more often in experimental animals than in humans. Rats that ate or drank barium over short periods had swelling and irritation of the intestines, changes in organ weights, decreased body weight, and increased numbers of deaths. Rats and mice that drank barium over long periods had damage to the kidneys, decreases in body weight, and decreased survival. We have no information about the ability of barium to affect reproduction in humans; a study in experimental animals did not find reproductive effects.

Some studies of humans and experimental animals exposed to barium in the air have reported damage to the lungs, but other studies have not found these effects. We have no reliable information about the health effects in humans or experimental animals that are exposed to barium by direct skin contact.

Barium has not been shown to cause cancer in humans or in experimental animals drinking barium in water. The Department of Health and Human Services and the International Agency for Research on Cancer have not classified barium as to its carcinogenicity. The EPA has

determined that barium is not likely to be carcinogenic to humans following ingestion and that there is insufficient information to determine whether it will be carcinogenic to humans following inhalation exposure.

More information on the health effects of barium can be found in Chapter 3.

1.6 HOW CAN BARIUM AFFECT CHILDREN?

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

We do not know whether children will be more or less sensitive than adults to barium toxicity. A study in rats that swallowed barium found a decrease in newborn body weight; we do not know if a similar effect would be seen in humans.

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

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

The greatest potential source of barium exposure is through food and drinking water. However, the amount of barium in foods and drinking water are typically too low to be of concern.

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

There is no routine medical test to determine whether you have been exposed to barium. Doctors can measure barium in body tissues and fluids, such as bones, blood, urine, and feces, using very complex instruments. These tests cannot be used to predict the extent of the exposure or potential health effects. This is normally done only for cases of severe barium poisoning and for medical research.

More information on testing for barium exposure is found in Chapters 3 and 7.

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

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

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

Recommendations and regulations are also updated periodically 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 barium include the following:

The EPA has determined that drinking water should not contain more than 2.0 milligrams (mg) barium per liter (L) of water (2.0 mg/L).

OSHA has a legally enforceable occupational exposure limit of 0.5 mg of soluble barium compounds per cubic meter (m^3) of air averaged over an 8-hour work day. The OSHA 8-hour exposure limit for barium sulfate dust in air is 15 mg/m^3 for total dust. NIOSH considers

exposure to barium chloride levels of 50 mg/m^3 and higher as immediately dangerous to life or health.

More information on government regulations can be found in Chapter 8.

1.10 WHERE CAN I GET MORE INFORMATION?

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

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

Toxicological profiles are also available on-line at www.atsdr.cdc.gov and on CD-ROM. You may request a copy of the ATSDR ToxProfiles™ CD-ROM by calling the toll-free information and technical assistance number at 1-800-CDCINFO (1-800-232-4636), by e-mail at cdcinfo@cdc.gov, or by writing to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine
1600 Clifton Road NE
Mailstop F-32
Atlanta, GA 30333
Fax: 1-770-488-4178

Organizations for-profit may request copies of final Toxicological Profiles from the following:

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

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO BARIUM IN THE UNITED STATES

Barium is an alkaline earth metal, principally found as barite (barium sulfate) and witherite (barium carbonate) ores. Barium and barium compounds have a variety of uses including as getters in electronic tubes (barium alloys), rodenticide (barium carbonate), colorant in paints (barium carbonate and barium sulfate), and x-ray contrast medium (barium sulfate). Barium naturally occurs in food and groundwater. Barium concentrations in drinking water in the United States typically average 30 µg/L, but can average as high as 302 µg/L. However, individuals residing in certain regions of Kentucky, northern Illinois, New Mexico, and Pennsylvania who rely on groundwater for their source of drinking water may be exposed to barium concentrations as high as 10 times the maximum contaminant level (MCL) in drinking water of 2.0 mg/L. Low levels of barium are also found in ambient air; levels are typically less than 0.05 µg barium/m^3.

There is little quantitative information regarding the extent of barium absorption following inhalation, oral, or dermal exposure. Available evidence indicates that barium is absorbed to some extent following inhalation, oral, and dermal exposure; however, in some cases, absorption is expected to be limited. For example, there is some evidence that gastrointestinal absorption of barium in humans is <5–30% of the administered dose. The general population can be exposed to barium via inhalation, oral, or dermal exposure; under most circumstances, oral exposure would be the predominant route of exposure.

2.2 SUMMARY OF HEALTH EFFECTS

An important factor affecting the development of adverse health effects in humans is the solubility of the barium compound to which the individual is exposed. Soluble barium compounds would generally be expected to be of greater health concern than insoluble barium compounds because of their greater potential for absorption. The various barium compounds have different solubilities in water and body fluids and therefore serve as variable sources of the Ba^{2+} ion. The Ba^{2+} ion and the soluble compounds of barium (notably chloride, nitrate, hydroxide) are toxic to humans. Although barium carbonate is relatively insoluble in water, it is toxic to humans because it is soluble in the gastrointestinal tract. The insoluble compounds of barium (notably sulfate) are inefficient sources of Ba^{2+} ion and are therefore generally nontoxic to humans. The insoluble, nontoxic nature of barium sulfate has made it practical to use this particular barium compound in medical applications as a contrast media for x-ray examination of

the gastrointestinal tract. Barium provides an opaque contrasting medium when ingested or given by enema prior to x-ray examination. Under these routine medical situations, barium sulfate is generally safe. However, barium sulfate or other insoluble barium compounds may potentially be toxic when it is introduced into the gastrointestinal tract under conditions where there is colon cancer or perforations of the gastrointestinal tract and barium is able to enter the blood stream.

There are a number of reports of serious health effects in individuals intentionally or accidentally exposed to barium carbonate or chloride. The predominant effect is hypokalemia, which can result in ventricular tachycardia, hypertension and/or hypotension, muscle weakness, and paralysis. Barium is a competitive potassium channel antagonist that blocks the passive efflux of intracellular potassium, resulting in a shift of potassium from extracellular to intracellular compartments. The net result of this shift is a significant decrease in the potassium concentration in the blood plasma. Although the case reports did not provide information on doses, it is likely that the doses were high. In addition to the effects associated with hypokalemia, gastrointestinal effects such as vomiting, abdominal cramps, and watery diarrhea are typically reported shortly after ingestion. Similar effects have been reported in cases of individuals exposed to very high concentrations of airborne barium; the effects include electrocardiogram (ECG) abnormalities, muscle weakness and paralysis, hypokalemia, and abdominal cramps, nausea, and vomiting.

Several investigators have examined whether exposure to much lower doses of barium would adversely affect the cardiovascular system. A population-based study found significant increases in the risk of death from cardiovascular disease among residents 65 years of age and older living in communities with high levels of barium in the drinking water. However, these data cannot be used to establish a causal relationship because the study did not control for other cardiovascular risk factors or the use of water softeners, which would decrease barium levels and increase sodium levels. Two other studies did not find alterations in blood pressure and cardiac rhythm. In general, animal studies designed to assess cardiovascular function have not found significant alterations in blood pressure or ECG readings following low-dose oral exposure. One study did find significant increases in blood pressure in rats exposed to 0.80 mg barium/kg/day. However, the use of a low mineral diet with less than adequate levels of calcium may have influenced the study results.

The available animal data provide strong evidence that the most sensitive adverse effect of barium is renal toxicity. There are some reports of renal effects in case reports of individuals ingesting high doses of barium. Nephropathy has been observed in rats and mice following long-term oral exposure to barium.

In both species, there is a steep dose-response curve for the incidence of nephropathy. For example, nephropathy was not observed in mice exposed to 205 mg barium/kg/day for an intermediate duration; at 450 mg barium/kg/day, 95% of the animals exhibited mild to moderate nephropathy. Data in mice also suggest that the severity and sensitivity to renal lesions is related to duration of exposure. As noted previously, a 205 mg barium/kg/day dose is a no effect level in mice exposed to barium chloride for 90 days; a 2-year exposure to 200 mg barium/kg/day resulted in moderate to marked nephropathy.

The potential for barium to induce reproductive and developmental effects has not been well investigated. Decreases in the number of sperm and sperm quality and a shortened estrous cycle and morphological alterations in the ovaries were observed in rats exposed to 2.2 mg barium/m^3 and higher in air for an intermediate duration. Interpretation of these data is limited by the poor reporting of the study design and results, in particular, whether the incidence was significantly different from controls. In general, oral exposure studies have not found morphological alterations in reproductive tissues of rats or mice exposed to 180 or 450 mg barium/kg/day, respectively, as barium chloride in drinking water for an intermediate duration. Additionally, no significant alterations in reproductive performance was observed in rats or mice exposed to 200 mg barium/kg/day as barium chloride in drinking water. Decreased pup birth weight and a nonsignificant decrease in litter size have been observed in the offspring of rats exposed to 180/200 mg barium/kg/day as barium chloride in drinking water prior to mating.

Several studies have examined the carcinogenic potential of barium following oral exposure and did not find significant increases in the tumor incidence. No studies have adequately assessed the carcinogenicity of barium following inhalation exposure. The Department of Health and Human Services (DHHS) and the International Agency for Research on Cancer (IARC) have not assessed the carcinogenicity of barium. The EPA has concluded that barium is not classifiable as to human carcinogenicity, Group D. However, under EPA's revised guidelines for carcinogen risk assessment, barium is considered not likely to be carcinogenic to humans following oral exposure and its carcinogenic potential cannot be determined following inhalation exposure.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for barium. 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.

Inhalation MRLs

No acute-, intermediate-, or chronic-duration inhalation MRLs were derived for barium because studies evaluating the effects of barium in humans and animals following acute, intermediate, and chronic inhalation exposure were inadequate for establishing the exposure concentrations associated with adverse health effects. Five reports of occupational exposure to barium have been identified. In one study (Doig 1976), a benign pneumoconiosis was observed in several workers exposed to barium sulfate; two other studies did not find barium-related alterations in the respiratory tract of workers exposed to barium sulfate (Seaton et al. 1986) or barium carbonate (Essing et al. 1976). Other effects reported in the occupational exposure studies were an increase in blood pressure (Essing et al. 1976), gastrointestinal distress, muscle weakness and paralysis, absence of deep tendon reflex, and decreased serum potassium levels in a worker exposed to barium carbonate powder (Shankle and Keane 1988). A fifth study did not find alterations in plasma potassium levels in welders using barium-containing electrodes (Zschiesche et al. 1992). Interpretation of these studies is limited by the small number of subjects, possible lack of a control group, and/or the lack of quantitative exposure information.

Three animal studies evaluating the toxicity of inhaled barium have also been identified. Two of the studies reported adverse respiratory tract effects including lung lesions (perivascular and peribronchial sclerosis and focal thickening of the intraalveolar septa) in rats exposed to 3.6 mg barium/m^3 as barium carbonate dust 4 hours/day, 6 days/week for 4 months (Tarasenko et al. 1977) and bronchoconstriction in guinea pigs exposed to 0.06 mg barium/m^3/minute as barium chloride for an unspecified amount of time

(Hicks et al. 1986). The third study (Cullen et al. 2000) did not find histological alterations in the lungs of rats exposed to 44.1 mg barium/m^3 as barium sulfate for 7 hours/day, 5 days/week for 119 days. Increases in blood pressure were observed in the Tarasenko et al. (1977) and Hicks et al. (1986) studies. Tarasenko et al. (1977) also reported hematological, reproductive, and developmental effects in rats exposed to barium carbonate dust. None of these studies provide a suitable basis for an inhalation MRL. The Tarasenko et al. (1977) studies are limited by poor reporting of the study design and results, lack of incidence data, and lack of statistical analysis for many of the end points. The Hicks et al. (1986) study did not report the frequency or length of exposure, the number of animals used was not clearly reported, and it does not appear that control animals were used. Although the Cullen et al. (2000) study was well reported and designed, it only examined the respiratory tract and did not identify an adverse effect level. Oral exposure studies identify the kidney as the most sensitive target of toxicity; this end point was not evaluated in the Cullen et al. (2000) study.

Oral MRLs

There are numerous case reports of individuals intentionally or accidentally ingesting unreported but presumably high doses of barium (Das and Singh 1970; Deng et al. 1991; Diengott et al. 1964; Downs et al. 1995; Gould et al. 1973; Jha et al. 1993; Koch et al. 2003; Lewi and Bar-Khayim 1964; McNally 1925; Ogen et al. 1967; Phelan et al. 1984; Silva 2003; Talwar and Sharma 1979; Wetherill et al. 1981). The consistently observed effects included abdominal distress (vomiting, abdominal cramping, and watery diarrhea), numbness around the face, muscle weakness, paralysis, and ventricular tachycardia.

Information on the acute oral toxicity of barium is limited to two studies in rats conducted by Borzelleca et al. (1988). A nonsignificant increase in mortality (3/20 females compared to 0/20 in controls) was found in rats receiving gavage doses of 198 mg barium/kg/day as barium chloride in water for 10 days. In the other study conducted by this group, 15/20 animals died after a single dose of 198 mg barium/kg/day as barium chloride in water. In the 10-day study, significant decreases in relative kidney weight (kidney:brain ratio) were observed in female rats administered 66–138 mg barium/kg/day and decreases in blood urea nitrogen (BUN) levels were observed in female rats dosed with 66–198 mg barium/kg/day and male rats dosed with 198 mg barium/kg/day. The magnitude of change in BUN levels was small (less than 15%) and was not dose-related; the decrease in BUN was not considered to be biologically significant. Additionally, BUN levels are typically increased in response to kidney damage. Significant decreases in absolute ovary weight and relative ovary weight (ovary:brain ratio) were observed at 198 mg barium/kg/day in the 10-day study. The biological significance of this change in organ weight is

questionable; no gross alterations in the ovaries were observed in this study and no histological alterations were observed in rats or mice exposed to barium chloride for acute, intermediate, or chronic durations to barium doses as high as 180 mg barium/kg/day in rats (NTP 1994) and 495 mg barium/kg/day in mice (NTP 1994).

The data are considered inadequate for derivation of an acute-duration oral MRL for barium. The available animal studies (Borzelleca et al. 1988) have evaluated the toxicity of barium chloride in repeated dose studies; however, neither study identified a non-lethal biologically significant adverse effect level. Longer-term studies identify the kidney as the most sensitive target; however, it is not known if the kidney would also be the most sensitive target following acute-duration exposure. Data in mice suggest that the severity and sensitivity to renal lesions are related to duration of exposure. The intermediate-duration mouse study identified a NOAEL of 205 mg barium/kg/day; however; a 2-year exposure to 200 mg barium/kg/day resulted in moderate to marked nephropathy (NTP 1994). Derivation of an MRL using the highest identified no-observed-adverse-effect level (NOAEL) is not recommended at this time because critical targets of toxicity and dose-response relationships have not been established for this exposure category. The exposure levels are poorly characterized in the available reports of human poisonings, acute-duration animal studies have failed to identify the critical target of barium toxicity, and it is possible that the critical target (kidneys) following long-term exposure may not be a sensitive target following short-term exposure.

- An MRL of 0.2 mg barium/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to barium.

Information on the oral toxicity of barium in humans following intermediate-duration oral exposure is limited to an experimental study in which men were exposed to 0.1 or 0.2 mg barium/kg/day as barium chloride in drinking water for 4 weeks (Wones et al. 1990). No significant alterations in blood pressure or ECG readings, relative to initial baseline measurements, were found.

A number of animal studies have evaluated barium toxicity following intermediate-duration oral exposure. Several of these studies focused on the cardiovascular system or assessed cardiovascular function. Perry et al. (1983, 1985, 1989) reported significant increases in blood pressure in rats administered 8.6 or 11 mg barium/kg/day as barium chloride in drinking water for 1 or 4 months, respectively. NTP (1994) and McCauley et al. (1985) did not find significant alterations in blood pressure or ECG readings in rats exposed to 150 or 180 mg barium/kg/day in drinking water for 13 or 16 weeks, respectively. The reason for the differences between the results from the Perry et al. (1983, 1985, 1989)

studies and the NTP (1994) and McCauley et al. (1985) studies is not known. It is possible that the low-mineral diet used in the Perry et al. (1983, 1985, 1989) studies influenced the results. The calcium content of the rye-based diet was 3.8 mg/kg, which is lower than the concentration recommended for maintenance, growth, and reproduction of laboratory rats (NRC 1995b).

The results of the McCauley et al. (1985) and NTP (1994) studies suggest that the kidney is the most sensitive target of toxicity in rats and mice. In the McCauley et al. (1985) study, glomerular alterations consisting of fused podocytes and thickening of the capillary basement membrane were found in uninephrectomized Sprague Dawley rats, Dahl salt-sensitive rats, and Dahl salt-resistant rats exposed to 150 mg barium/kg/day in drinking water for 16 weeks. In the NTP (1994) 13-week rat study, significant increases in absolute and relative kidney weights were observed in female rats exposed to 115 or 180 mg barium/kg/day and in males exposed to 200 mg barium/kg/day. At 200 and 180 mg barium/kg/day, minimal to mild dilatation of the proximal convoluted tubules of the outer medulla and renal cortex was observed in the males and females, respectively; an increase in mortality (30%) was also observed in the males exposed to 200 mg barium/kg/day. In mice, mild to moderate nephropathy (characterized as tubule dilatation, regeneration, and atrophy) was observed in 100% of the males exposed to 450 mg barium/kg/day and 90% of the females exposed to 495 mg barium/kg/day; no renal lesions were observed at the next lowest dose level (205 and 200 mg barium/kg/day in males and females, respectively). Other effects observed at the 450/495 mg barium/kg/day dose level included weight loss, spleen and thymus atrophy, and increased mortality (60% of the males and 70% of females died after 5 weeks of exposure).

Other end points that have been examined in rats and mice include neurotoxicity, reproductive toxicity, and developmental toxicity. In male and female rats, slight decreases in undifferentiated motor activity were observed at 10 mg barium/kg/day and higher. However, the difference between motor activity in the barium-exposed rats and the controls was less than 20% and was not considered to be biologically significant. At 180 mg barium/kg/day, the difference was 30% in the female rats, which was considered to be adverse. No significant alterations were found on the remaining neurobehavioral tests (grip strength, tail flick latency, startle response, and hindlimb foot splay). In mice, a significant decrease in forelimb grip strength was observed in females exposed to 495 mg barium/kg/day; this may have been due to debilitation. No other alterations in neurobehavioral performance were found. No effects on reproductive tissues or reproductive performance were observed in rats or mice exposed to approximately 200 mg barium/kg/day (Dietz et al. 1992; NTP 1994). Pre-mating exposure of male and female rats to 180/200 mg barium/kg/day resulted in decreased pup birth weight and a nonsignificant decrease in litter size; the NOAEL for these effects was 110/115 mg barium/kg/day (Dietz et al. 1992). No developmental

effects were observed in mice exposed to 200 mg barium/kg/day (Dietz et al. 1992). Another study (Tarasenko et al. 1977) also reported developmental effects (increased offspring mortality during the first 2 months and disturbances in liver function) in an unspecified animal species; however, the lack of information on experimental methods, exposure conditions, and results limits the usefulness of this study for evaluating the potential of aluminum to induce developmental toxicity.

Based on these data, the kidney appears to be the most sensitive target following intermediate-duration oral exposure to barium. Three studies identified adverse effect levels for kidney effects: (1) a lowest-observed-adverse-effect level (LOAEL) of 150 mg barium/kg/day was identified in uninephrectomized and salt-sensitive and salt resistant rats (McCauley et al. 1985), (2) a LOAEL of 115 mg barium/kg/day was identified for increased kidney weight in rats; the NOAEL was 65 mg barium/kg/day (NTP 1994), and (3) a LOAEL of 450 mg barium/kg/day for nephropathy in mice; the NOAEL was 205 mg barium/kg/day (NTP 1994). The NTP (1994) 13-week rat study, which identified the lowest LOAEL for a kidney effect, was selected as the basis of the intermediate-duration oral MRL; the change in kidney weight was considered an early indicator of potentially more serious effects in the kidney.

In this study (NTP 1994), groups of 10 male and 10 female F344/N rats were administered 0, 125, 500, 1,000, 2,000, or 4,000 ppm barium chloride dihydrate (0, 10, 30, 65, 110, and 200 mg barium/kg/day for males and 0, 10, 35, 65, 115, and 180 mg barium/kg/day for females) in drinking water for 90 days. Exposure-related deaths were observed during the last week of the study in 30% of the males and 10% of the females exposed to 200/180 mg barium/kg/day. Significant decreases in final body weights were observed in the 200 mg barium/kg/day males (13% lower than controls) and 180 mg barium/kg/day females (8% lower than controls); significant decreases in water consumption (approximately 30% lower than controls) were also observed at this dose level. Significant increases in absolute and relative kidney weights were observed in females exposed to 115 or 180 mg barium/kg/day and increases in relative kidney weights were also observed in males at 200 mg barium/kg/day; an increase in relative kidney weight was also observed in the females exposed to 65 mg barium/kg/day; The magnitude of the increases in relative kidney weights were 7, 14, and 19% in the females exposed to 65, 115, and 180 mg barium/kg/day and 12% in males exposed to 200 mg barium/kg/day. Minimal to mild, focal to multifocal dilatation of the proximal renal cortex was observed in three male and three female rats in the 200/180 mg barium/kg/day group. The small increase in relative kidney weight (7%) observed in the female rats exposed to 65 mg barium/kg/day was not considered biologically significant because it is not supported by an increase in histological alterations in the kidney at 65 or 115 mg barium/kg/day or in rats exposed

to 75 mg barium/kg/day for 2 years (NTP 1994). Thus, this study identifies a NOAEL of 65 mg barium/kg/day and a LOAEL of 115 mg barium/kg/day.

A NOAEL/LOAEL approach was used to derive the MRL because none of the available benchmark dose models provided an adequate fit to the absolute or relative kidney weight data. Thus, the intermediate-duration oral MRL of 0.2 mg barium/kg/day was calculated by dividing the NOAEL of 65 mg barium/kg/day by an uncertainty factor of 100 (10 to account for animal to human extrapolation and 10 for human variability) and a modifying factor of 3. The modifying factor of 3 was included to account for deficiencies in the oral toxicity database, particularly the need for an additional developmental toxicity study. Decreases in pup birth weight and a nonstatistically significant decrease in live litter size were observed in the offspring of rats exposed to 180/200 mg Ba/kg/day as barium chloride in drinking water prior to mating (Dietz et al. 1992). Maternal body weight gain and water consumption were not reported, thus it is not known if the decreases in pup body weight were secondary to maternal toxicity or direct effect on the fetus. No developmental effects were observed in mice at the highest dose tested (200 mg Ba/kg/day) (Dietz et al. 1992). One other study examined the potential for developmental toxicity in orally exposed animals (Tarasenko et al. 1977). However, because the study was poorly reported and no incidence data or statistical analysis were presented in the published paper, the reported findings of increased mortality and systemic toxicity in the offspring of an unspecified species orally exposed to barium during conception and pregnancy can not be adequately evaluated. The Dietz et al. (1992) study was designed to be a mating trial and did not expose the animals during gestation; thus, database is lacking an adequate study to evaluate the potential for barium to induce developmental effects.

- An MRL of 0.2 mg barium/kg/day has been derived for chronic-duration oral exposure (>365 days) to barium.

Several human and animal studies have examined the toxicity of barium following chronic-duration exposure. Two community-based studies have evaluated the possible association between elevated levels of barium in drinking water and increased risk of cardiovascular disease. No significant alterations in blood pressure measurements or increases in the prevalence of hypertension, heart disease, or stroke were found among residents of two communities with elevated (0.2 mg barium/kg/day) or low (0.003 mg barium/kg/day) levels of barium in drinking water (Brenniman and Levy 1985; Brenniman et al. 1979a, 1981). In the second study, significantly higher mortality rates, particularly among individuals 65 years of age and older, for cardiovascular disease and heart disease (arteriosclerosis) were found in a community with elevated barium drinking water levels (0.06–0.3 mg barium/kg/day) as compared to a community with low barium levels (0.006 mg barium/kg/day) (Brenniman and Levy 1985; Brenniman et

al. 1979a, 1981). A common limitation of both studies is the lack of information on tap water consumption, actual barium intakes, and duration of exposure. Additionally, the second study did not control for a number of potential confounding variables, particularly the use of water softeners, which would have resulted in a decrease in barium levels in the drinking water and an increase in sodium levels.

Significant increases in blood pressure were observed in rats exposed to 0.8 mg barium/kg/day as barium chloride in drinking water for 16 months (Perry et al. 1983, 1985, 1989); the NOAEL for this effect was 0.17 mg barium/kg/day. At higher doses (7.2 mg barium/kg/day), depressed rates of cardiac contraction, reduced cardiac electrical conductivity, and decreased cardiac ATP levels were observed. As noted in the discussion of the intermediate-duration oral MRL, interpretation of the results of this study is limited due to the low mineral diet, which may have supplied inadequate levels of calcium. No adverse effects were observed in rats exposed to 60 mg barium/kg/day as barium chloride in drinking water for 2 years (NTP 1994), 15 mg barium/kg/day to an unspecified barium compound in drinking water for 68 weeks (McCauley et al. 1985), or 0.7 mg barium/kg/day as barium acetate in drinking water for a lifetime (Schroeder and Mitchener 1975a). In mice exposed to barium chloride in drinking water for 2 years, marked renal nephropathy was observed at 160 mg barium/kg/day; the increased incidence of nephropathy in the next lowest dose group (75 mg barium/kg/day) was not statistically significant. Other adverse effects observed at 160 mg barium/kg/day included weight loss and increased mortality (NTP 1994).

As with intermediate-duration exposure, the animal data provide suggestive evidence that the kidney is the most sensitive target of toxicity. A serious LOAEL of 160 mg barium/kg/day was identified for nephropathy in mice (NTP 1994); the NOAEL identified in this study is 75 mg/kg/day. Although no kidney lesions were observed in rats exposed to doses as high as 60 mg barium/kg/day (NTP 1994), the doses utilized in the study may not have been high enough to cause kidney damage. Biologically significant kidney alterations were observed at 115 mg barium/kg/day and higher in rats exposed for an intermediate duration (NTP 1994). The chronic-duration mouse study (NTP 1994) was selected as the basis of the chronic-duration MRL for barium.

In this study (NTP 1994), groups of 60 male and 60 female B6C3F1 mice were exposed to 0, 500, 1,250, or 2,500 ppm barium chloride dehydrate (0, 30, 75, and 160 mg barium/kg/day for males and 0, 40, 90, and 200 mg barium/kg/day for females) in drinking water for 2 years. Increased mortality attributed to renal lesions was observed in the 160/200 mg/kg/day group. Decreased body weights (<7%) were observed in the barium-exposed mice. The investigators noted that a moderate to marked weight loss was

observed in animals dying early. No significant alterations in hematology or clinical chemistry parameters were observed. A significant increase in the incidence of nephropathy was observed in male and female mice exposed to 160/200 mg/kg/day. The nephropathy was characterized by extensive regeneration of cortical and medullary tubule epithelium, tubule dilatation, hyaline cast formation, multifocal interstitial fibrosis, and glomerulosclerosis in some kidneys. The average severity of the nephropathy was 3.6 (moderate to marked) for both the males and females in the 160/200 mg/kg/day group.

A benchmark analysis of the incidence data for nephropathy in mice was conducted; details of this analysis are presented in Appendix A. A benchmark dose (BMD) of 80.06 mg barium/kg/day, which corresponds to a 5% increase in the incidence of nephropathy was calculated; the 95% lower confidence limit on the BMD (BMDL) was 61.13 mg barium/kg/day. The $BMDL_{05}$ was selected as the point of departure for deriving the chronic-duration oral MRL. The dose corresponding to a predicted 5% incidence was selected over the typically 10% incidence as a precaution due to the severity of the observed effects (moderate to marked severity nephropathy), which resulted in marked weight loss and increased mortality. Thus, the chronic-duration oral MRL of 0.2 mg barium/kg/day is based on the $BMDL_{05}$ of 61 mg barium/kg/day in male mice and an uncertainty factor of 100 (10 to account for animal to human extrapolation and 10 for human variability) and a modifying factor of 3. The modifying factor of 3 was included to account for deficiencies in the oral toxicity database, particularly the need for an additional developmental toxicity study. Decreases in pup birth weight and a nonstatistically significant decrease in live litter size were observed in the offspring of rats exposed to 180/200 mg Ba/kg/day as barium chloride in drinking water prior to mating (Dietz et al. 1992). Maternal body weight gain and water consumption were not reported, thus it is not known if the decreases in pup body weight were secondary to maternal toxicity or direct effect on the fetus. No developmental effects were observed in mice at the highest dose tested (200 mg Ba/kg/day) (Dietz et al. 1992). One other study examined the potential for developmental toxicity in orally exposed animals (Tarasenko et al. 1977). However, because the study was poorly reported and no incidence data or statistical analysis were presented in the published paper, the reported findings of increased mortality and systemic toxicity in the offspring of an unspecified species orally exposed to barium during conception and pregnancy can not be adequately evaluated. The Dietz et al. (1992) study was designed to be a mating trial and did not expose the animals during gestation; thus, database is lacking an adequate study to evaluate the potential for barium to induce developmental effects.

2. RELEVANCE TO PUBLIC HEALTH

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3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of barium. 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.

When evaluating the health effects of barium compounds, it is important to keep in mind that different barium compounds have different solubilities in water and body fluids and therefore serve as variable sources of the Ba^{2+} ion. The Ba^{2+} ion and the soluble compounds of barium (notably chloride, nitrate, and hydroxide) are generally highly toxic to humans and experimental animals. The insoluble barium compounds (notably sulfate) are inefficient sources of the Ba^{2+} ion and therefore are generally nontoxic. Although barium carbonate is insoluble in water, barium ions would be released from ingested barium carbonate in the acid milieu of the stomach. Throughout the following section (3.2), the health effects by route of exposure of both soluble and insoluble barium compounds are discussed.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a

considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

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

3.2.1 Inhalation Exposure

Studies evaluating the effects of barium following acute, intermediate, and chronic inhalation exposure are limited to several case reports of humans exposed occupationally (Doig 1976; Essing et al. 1976; Seaton et al. 1986; Shankle and Keane 1988), an experimental exposure to barium in welding fumes (Zschiesche et al. 1992), and three experimental studies with animals (Cullen et al. 2000; Hicks et al. 1986; Tarasenko et al. 1977). These case reports and animal studies are not adequate for firmly establishing the health effects of barium by inhalation because of a number of significant study limitations. The case reports are generally inadequate because data were available for a limited number of exposed subjects and because exposure conditions (duration, frequency, dose) were not well characterized (Doig 1976; Essing et al. 1976; Seaton et al. 1986; Shankle and Keane 1988). One of the animal studies was limited in that apparently no control animals were used, an inhalation chamber providing a controlled dose and environment was not used, and there was a lack of information regarding

the vehicle used, purity of the test material, duration and frequency of exposure, and number of animals tested (Hicks et al. 1986). The second animal study consisted of several experiments, but was generally limited in that the authors provided few details regarding experimental methods, exposure conditions, and test results, and no information as to the number of animals tested, purity of the test material, or statistical methods used; furthermore, in some experiments, it was not clear whether or not control animals were used (Tarasenko et al. 1977). The third study examined a limited number of end points (Cullen et al. 2000). In view of the major limitations associated with the available case reports and studies, results from these reports should be regarded as providing only preliminary and/or suggestive evidence that acute, intermediate, and chronic inhalation exposure to barium may potentially be associated with adverse health effects. Findings from the various case reports and animal studies are briefly described below.

3.2.1.1 Death

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

3.2.1.2 Systemic Effects

No studies were located regarding endocrine, dermal, or ocular effects in humans or animals after inhalation exposure to barium.

Respiratory Effects. Two reports of workers exposed chronically to dust from barium sulfate demonstrated that this exposure had a minor effect on the lungs. In one study, a benign pneumoconiosis was observed in several factory workers (Doig 1976). In a second study in which workers were exposed by mining barium sulfate, silicosis was observed but was attributed to inhalation of quartz (Seaton et al. 1986). In contrast, a study of workers chronically exposed to barium carbonate dust reported no respiratory symptoms attributable to barium exposure (Essing et al. 1976). X-ray analysis of the lungs also showed no abnormalities attributable to barium dust.

Studies regarding respiratory effects in animals following inhalation exposure to barium are limited to three reports (Cullen et al. 2000; Hicks et al. 1986; Tarasenko et al. 1977). Pulmonary lesions (perivascular and peribronchial sclerosis and focal thickening of the interalveolar septa) were observed in rats exposed to 3.6 mg barium/m^3 as barium carbonate dust 4 hours/day, 6 days/week for 4 months (Tarasenko et al. 1977). Bronchoconstriction was reportedly noted in guinea pigs following inhalation for an unspecified period of time to 0.06 mg barium/m^3/minute as aerosolized barium chloride solution

(Hicks et al. 1986). In contrast to these finding, no adverse histological alterations were observed in the lungs of rats exposed to 44.1 mg barium/m^3 as barium sulfate for 119 days (Cullen et al. 2000).

Cardiovascular Effects. Three of 12 workers chronically exposed to barium carbonate dust had elevated blood pressure and 2 workers had ECG abnormalities (Essing et al. 1976). However, it is unknown whether this represented an increased incidence because no comparison with a control population was performed. Increased blood pressure and cardiac irregularities were reportedly observed in guinea pigs exposed by inhalation for an unspecified period of time to 0.06 mg barium/m^3/minute as aerosolized barium chloride solution (Hicks et al. 1986). Tarasenko et al. (1977) reported a 32% increase in arterial pressure and alterations in ECG readings suggestive of disturbances in heart conductivity following proserine administration in rats exposed to 3.6 mg barium/m^3 as barium carbonate; no ECG alterations were observed prior to proserine administration.

Gastrointestinal Effects. Abdominal cramps, nausea, and vomiting were experienced by a 22-year-old factory worker accidentally exposed by acute inhalation to a large but unspecified amount of barium carbonate powder (Shankle and Keane 1988). No animal studies were located regarding gastrointestinal effects in animals after inhalation exposure to barium.

Hematological Effects. Altered hematological parameters were observed in rats following inhalation for an intermediate exposure period to 3.6 mg barium/m^3 as barium carbonate dust (Tarasenko et al. 1977). Reported changes included decreased blood hemoglobin and thrombocyte count.

Musculoskeletal Effects. After accidental exposure to a large amount of barium carbonate powder by acute inhalation, a 22-year-old factory worker developed progressive muscle weakness and paralysis of the extremities and neck (Shankle and Keane 1988); this is likely due to the low serum potassium level rather than a direct effect on muscle tissue. X-ray analysis of the bones and skeletal muscles of the pelvis and thighs of workers chronically exposed to barium carbonate dust revealed no apparent build up of insoluble barium in these tissues (Essing et al. 1976). No studies were located regarding musculoskeletal effects in animals after inhalation exposure to barium.

Hepatic Effects. No studies were located regarding hepatic effects in humans after inhalation exposure to barium. Impaired detoxifying function of the liver was noted in rats exposed to 3.6 mg barium/m^3 as barium carbonate dust (Tarasenko et al. 1977). No other details were reported.

Renal Effects. Renal failure occurred in a 22-year-old worker accidentally exposed by acute inhalation to barium carbonate powder (Shankle and Keane 1988). No studies were located regarding renal effects in animals after inhalation exposure to barium.

Body Weight Effects. A 21% decrease in body weight gain was observed in rats exposed to 3.6 mg barium/m^3 as barium carbonate dust for 4 months (Tarasenko et al. 1977).

Metabolic Effects. Decreases in plasma potassium concentrations were observed in two groups of welders using barium-containing electrodes; the barium levels in the work environment were 4.4 and 0.3 mg/m^3 (Zschiesche et al. 1992). However, this was not observed in a third group of welders exposed to 2.0 mg barium/m^3. A low serum potassium level was also observed in a worker accidentally exposed to barium carbonate powder (Shankle and Keane 1988). Additionally, the plasma potassium concentrations were not statistically different from levels measured prior to barium exposure. Tarasenko et al. (1977) reported a decrease in urinary calcium levels and increased blood phosphorus levels in rats exposed to 3.6 mg barium/m^3 as barium carbonate dust for an intermediate duration (Tarasenko et al. 1977). This study also reported a decrease in blood glucose levels in barium-exposed rats.

3.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans or animals after inhalation exposure to barium.

3.2.1.4 Neurological Effects

Absence of deep tendon reflexes was observed in a 22-year-old man accidentally exposed by acute inhalation to barium carbonate powder (Shankle and Keane 1988); as noted previously, this is probably due to the barium-induced low potassium levels. No studies were located regarding neurological effects in animals after inhalation exposure to barium.

3.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after inhalation exposure to barium. Only one limited report was available regarding reproductive effects in animals following intermediate inhalation exposure to barium carbonate (Tarasenko et al. 1977). Disturbances in spermatogenesis, including decreased number of sperm, decreased percentage of motile sperm, and decreased osmotic

resistance of sperm, were reportedly observed in male rats exposed by inhalation for one cycle of spermatogenesis to 15.8 mg barium/m^3 as barium carbonate dust. The testicles of these treated rats reportedly had an increase in the number of ducts with desquamated epithelium and a reduced number of ducts with 12^{th}-stage meiosis. The condition of the testicles of treated rats returned to normal 30 days after cessation of barium carbonate treatment (Tarasenko et al. 1977). Similar observations were noted in a second experiment in which male rats were exposed by inhalation for an intermediate period to 3.6 mg barium/m^3 as barium carbonate dust. In a third experiment by the same authors, female rats exposed by inhalation for an intermediate period to 2.2 or 9.4 mg barium/m^3 as barium carbonate dust reportedly developed a shortened estrous cycle and alterations in the morphological structure of the ovaries.

3.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans after inhalation exposure to barium. Only one limited report was available regarding developmental effects in animals after intermediate inhalation exposure to barium (Tarasenko et al. 1977). Reduced survival, underdevelopment, lowered weight gain, and various hematologic alterations (erythropenia, leukocytosis, eosinophilia, neutrophilia) were reported in the offspring of female rats exposed by inhalation for an intermediate period to 2.2 or 9.4 mg barium/m^3 as barium carbonate dust (Tarasenko et al. 1977). No other significant details regarding this developmental study were reported.

3.2.1.7 Cancer

No studies were located regarding cancer in humans or animals after inhalation exposure to barium.

3.2.2 Oral Exposure

The majority of studies evaluating the health effects of barium are oral exposure studies. The available oral studies include numerous case reports of humans exposed orally to barium through accidental or intentional ingestion, several epidemiological and statistical investigations of humans exposed to drinking water containing barium, and various experimental animal studies involving acute, intermediate, or chronic exposure to barium either by gavage or by drinking water. Findings from the various oral studies are summarized below.

3.2.2.1 Death

Death has been reported in a number of case reports of accidental or intentional ingestion of barium salts. The cause of death was attributed to cardiac arrest, severe gastrointestinal hemorrhage, or unknown causes (Das and Singh 1970; Deng et al. 1991; Diengott et al. 1964; Downs et al. 1995; Jourdan et al. 2001; McNally 1925; Ogen et al. 1967; Talwar and Sharma 1979). Doses in these cases were not known.

In addition to case reports of death in humans, several studies have examined mortality rates in residents living in communities with elevated barium levels in the drinking water (Brenniman and Levy 1985; Brenniman et al. 1979a, 1979b, 1981; Elwood et al. 1974; Schroeder and Kraemer 1974). Two studies found no statistical correlations between barium concentrations in drinking water and total mortality and/or cardiovascular mortality rates in exposed populations (Elwood et al. 1974; Schroeder and Kraemer 1974). Interpretation of the study results are limited by the lack of information on exposure conditions (dose, duration, frequency) and the number of people exposed. Results of a third study indicated that relative to communities with little or no barium in drinking water, communities with elevated concentrations of barium in their drinking water had significantly higher mortality rates for all causes, heart disease, arteriosclerosis, and all cardiovascular disease (Brenniman and Levy 1985; Brenniman et al. 1979a, 1979b, 1981). This epidemiological study had a number of confounding variables, including possible use in the study population of home water softeners that would remove barium from the drinking water, inclusion of communities that had significant changes in population, lack of a way to control for length of time an individual lived in a community, and widely varying concentrations of other contaminants (calcium, sodium, magnesium) in the drinking water.

The LD_{50} values for barium chloride in rats range from 132 to 277 mg barium/kg (Borzelleca et al. 1988; Tardiff et al. 1980). Significant increases in mortality were observed in rats and mice exposed to 200 or 450 mg barium/kg/day as barium chloride in drinking water for 90 days (NTP 1994). Survival was not affected at 110 or 205 mg barium/kg/day in the rats or mice, respectively. No changes in mortality were observed in rats chronically exposed to doses as high as 60 mg barium/kg/day as barium chloride in the drinking water (NTP 1994). An increase in mortality, attributable to nephropathy, was observed in mice chronically exposed to 160 mg barium/kg/day as barium chloride in drinking water (NTP 1994); the number of deaths was similar to controls in mice exposed to 75 mg barium/kg/day. In male mice exposed to 0.95 mg barium/kg/day as barium acetate in drinking water, a significant decrease in longevity (defined as average lifespan of the last five surviving animals) was observed; however, no significant differences in mean lifespan were observed (Schroeder and Mitchener 1975b). Similarly, lifespan was not

significantly altered in female mice exposed to 0.95 mg barium/kg/day (Schroeder and Mitchener 1975b) or male or female rats exposed to 0.7 mg barium/kg/day as barium acetate in drinking water (Schroeder and Mitchener 1975a).

LD_{50} values and reliable LOAEL values for death in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.2 Systemic Effects

The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

Respiratory Effects. Limited data are available regarding respiratory effects in animals following oral barium exposure. Fluid in the trachea was observed in rats receiving a single gavage dose of 198 mg barium/kg as barium chloride (Borzelleca et al. 1988). However, this effect was not observed when rats were dosed with 198 mg barium/kg/day as barium chloride for 10 days (Borzelleca et al. 1988). No significant alterations in lung weights, gross lesions, or histopathological alterations were observed in the respiratory tracts of rats and mice exposed to doses as high as 110 or 70 mg barium/kg/day, 180 or 450 mg barium/kg/day, or 60 and 160 mg barium/kg/day for intermediate or chronic durations, respectively (McCauley et al. 1985; NTP 1994; Tardiff et al. 1980) or lifetime exposure to 0.7 or 0.95 mg barium/kg/day, respectively, as barium acetate via drinking water (Schroeder and Mitchener 1975a).

Cardiovascular Effects. As demonstrated in numerous case reports, acute exposure to presumably high doses of barium carbonate, barium sulfate, or barium chloride can result in serious effects on heart rhythm. Barium adversely affects cardiac automaticity resulting in ventricular tachycardia and other disruptions of rhythm (Deng et al. 1991; Diengott et al. 1964; Downs et al. 1995; Gould et al. 1973; Jha et al. 1993; Koch et al. 2003; Silva 2003; Talwar and Sharma 1979; Wetherill et al. 1981). Hypotension has also been reported in some cases (Koch et al. 2003; Talwar and Sharma 1979). The likely cause of these effects was barium-induced hypokalemia.

Several human studies have investigated a possible association between exposure to low levels of barium and alterations in blood pressure and cardiac rhythms. In a small-scale (11 subjects) study of individuals exposed to 0.1 or 0.2 mg barium/kg/day as barium chloride in drinking water for 4 weeks, no significant alterations in blood pressure or ECG readings were found (Wones et al. 1990). There was no significant

Table 3-1 Levels of Significant Exposure to Barium - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (Sprague-Dawley)	once (GW)				198 (death in 15/20 rats)	Borzelleca et al. 1988 Barium chloride	
2	Rat (Sprague-Dawley)	once (GW)				269 F (LD50 in females)	Borzelleca et al. 1988 Barium chloride	
3	Rat (NS)	once (GW)				132 (LD50 adult) 220 (LD50 weanling)	Tardiff et al. 1980 Barium chloride	
Systemic								
4	Rat (Sprague-Dawley)	10 d 1 x/d (GW)	Resp	198			Borzelleca et al. 1988 Barium chloride	
			Cardio	198				
			Gastro	198				
			Hemato	198				
			Hepatic	198				
			Renal	198				
			Ocular	198				
			Bd Wt	198				

Table 3-1 Levels of Significant Exposure to Barium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
5	Rat (Sprague-Dawley)	once (GW)	Resp	66	198 (fluid in trachea)		Borzelleca et al. 1988 Barium chloride	
			Cardio	198				
			Gastro	66	198 (inflammation of small and large intestine)			
			Hemato	198				
			Hepatic	66	198 (decreased liver/brain weight ratio; darkened liver)			
			Renal	66	198 (increased kidney/body weight ratio)			
			Ocular	66	198 (ocular discharge)			
			Bd Wt	66	198 (decreased body weight)			
			Other	198				
Immuno/ Lymphoret								
6	Rat (Sprague-Dawley)	10 d 1 x/d (GW)		198			Borzelleca et al. 1988 Barium chloride	Evaluated weight and occurrence of gross lesions in thymus.
Neurological								
7	Rat (Sprague-Dawley)	10 d 1 x/d (GW)		198			Borzelleca et al. 1988 Barium chloride	

Table 3-1 Levels of Significant Exposure to Barium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Reproductive								
8	Rat (Sprague-Dawley)	once (GW)		198			Borzelleca et al. 1988 Barium chloride	Evaluated testes and ovary weights.
9	Rat (Sprague-Dawley)	10 d 1 x/d (GW)		138 F	198 F (decreased ovary weight and ovaries/brain ratio)		Borzelleca et al. 1988 Barium chloride	Evaluated testes and ovary weights.
INTERMEDIATE EXPOSURE								
Death								
10	Rat (Fischer- 344)	90 d (W)				200 M (30% mortality)	NTP 1994 Barium chloride	
11	Mouse (B6C3F1)	90 d (W)				450 M (60% mortality)	NTP 1994 Barium chloride	
Systemic								
12	Human (NS)	4 wk 7 d/wk (W)	Cardio	0.2 M			Wones et al. 1990 Barium chloride	
13	Rat (Dahl)	16 wk (W)	Cardio	150			McCauley et al. 1985 NR	Study used salt resistant and salt sensitive rat strains.
			Renal	15	150 (fused podocytes and thickening of the capillary basement membrane in glomeruli)			

Table 3-1 Levels of Significant Exposure to Barium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
14	Rat (Sprague-Dawley)	16 wk (W)	Cardio	150			McCauley et al. 1985 NR	Study used uninephrecomized rats.
			Renal	15	150 (fused podocytes and thickening of the capillary basement membrane in glomeruli)			
15	Rat (Sprague-Dawley)	36 wk (W)	Resp	37.5 M			McCauley et al. 1985 NR	
			Cardio	37.5 M				
			Gastro	37.5 M				
			Musc/skel	37.5 M				
			Hepatic	37.5 M				
			Renal	37.5 M				
			Ocular	37.5 M				
			Bd Wt	37.5 M				

Table 3-1 Levels of Significant Exposure to Barium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
16	Rat (Sprague-Dawley)	46 wk (W)	Resp	37.5 F			McCauley et al. 1985 NR	
			Cardio	37.5 F				
			Gastro	37.5 F				
			Musc/skel	37.5 F				
			Hepatic	37.5 F				
			Renal	37.5 F				
			Ocular	37.5 F				
			Bd Wt	37.5 F				
17	Rat (Fischer- 344)	15 d (W)	Resp	110			NTP 1994 Barium chloride	
			Cardio	110				
			Gastro	110				
			Hemato	110				
			Hepatic	110				
			Renal	110				
			Bd Wt	110				
			Metab	110				

Table 3-1 Levels of Significant Exposure to Barium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
18	Rat (Fischer- 344)	90 d (W)	Resp	180 F			NTP 1994 Barium chloride	
			Cardio	180 F				
			Gastro	180 F				
			Hemato	180 F				
			Musc/skel	180 F				
			Hepatic	180 F				
			Renal	65[b] F	180 F (dilatation of proximal renal cortex)			
					115 F (increased kidney weight)			
			Ocular	180 F				
			Bd Wt	110 M	200 M (13% lower final body weight)			
			Metab	180 F				
19	Rat (Long- Evans)	1 mo 7 d/wk (W)	Cardio	1 F	8.6 F (increased blood pressure)		Perry et al. 1983, 1985, 1989 Barium chloride	Animals were fed a low mineral diet.
20	Rat (Long- Evans)	4 mo 7 d/wk (W)	Cardio	1.2 F	11 F (increased blood pressure)		Perry et al. 1983, 1985, 1989 Barium chloride	Animals were fed a low mineral diet.

Table 3-1 Levels of Significant Exposure to Barium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
21	Rat Charles-River	13 wk 7 d/wk (W)	Resp	35			Tardiff et al. 1980 Barium chloride	
			Cardio	35				
			Hemato	35				
			Musc/skel	35				
			Hepatic	35				
			Renal	35				
			Bd Wt	35				
22	Mouse (B6C3F1)	90 d (W)	Resp	450 M			NTP 1994 Barium chloride	
			Cardio	450 M				
			Gastro	450 M				
			Hemato	450 M				
			Musc/skel	450 M				
			Hepatic	450 M				
			Renal	205 M		450 M (nephropathy)		
			Ocular	450 M				
			Bd Wt	205 M		450 M (30% lower final body weight)		
			Metab	450 M				

Table 3-1 Levels of Significant Exposure to Barium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
23	Mouse (B6C3F1)	15 d (W)	Resp	70 M			NTP 1994 Barium chloride	
			Cardio	70 M				
			Gastro	70 M				
			Hemato	70 M				
			Hepatic	70 M				
			Renal	70 M				
			Bd Wt	70 M				
			Metab	70 M				
Immuno/ Lymphoret								
24	Rat (Sprague-Dawley)	36 wk (W)		37.5 M			McCauley et al. 1985 NR	Histological examination of thymus and lymph nodes.
25	Rat (Sprague-Dawley)	46 wk (W)		37.5 F			McCauley et al. 1985 NR	Histological examination of thymus and lymph nodes.
26	Rat (Fischer- 344)	90 d (W)		180 F			NTP 1994 Barium chloride	Histological examination of spleen and thymus.
27	Mouse (B6C3F1)	90 d (W)		205 M	450 M (thymic and splenic atrophy)		NTP 1994 Barium chloride	Histological examination of spleen and thymus.

Table 3-1 Levels of Significant Exposure to Barium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Neurological								
28	Rat (Sprague-Dawley)	36 wk (W)		37.5 M			McCauley et al. 1985 NR	Histological examination of brain.
29	Rat (Sprague-Dawley)	46 wk (W)		37.5 F			McCauley et al. 1985 NR	Histological examination of brain.
30	Rat (Fischer- 344)	90 d (W)		115 F	180 F (decreased spontaneous motor activity)		NTP 1994 Barium chloride	
31	Rat (Fischer- 344)	15 d (W)		110			NTP 1994 Barium chloride	
32	Rat Charles-River	13 wk 7 d/wk (W)		35			Tardiff et al. 1980 Barium chloride	Histological examination of brain.
33	Mouse (B6C3F1)	90 d (W)		200 F	495 F (decreased forelimb grip strength)		NTP 1994 Barium chloride	
34	Mouse (B6C3F1)	15 d (W)		70 M			NTP 1994 Barium chloride	
Reproductive								
35	Rat (Fischer- 344)	M: 60 d F: 30 d (W)		200 M 180[c] F			Dietz et al. 1992 Barium chloride	

Table 3-1 Levels of Significant Exposure to Barium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
36	Rat (Sprague-Dawley)	36 wk (W)		37.5 M			McCauley et al. 1985 NR	Histological examination of reproductive tissues.
37	Rat (Sprague-Dawley)	46 wk (W)		37.5 F			McCauley et al. 1985 NR	Histological examination of reproductive tissues.
38	Rat (Fischer- 344)	90 d (W)		200 M 180[c] F			NTP 1994 Barium chloride	Histological examination of reproductive tissues.
39	Rat (Fischer- 344)	15 d (W)		110			NTP 1994 Barium chloride	
40	Mouse (B6C3F1)	M: 60 d F: 30 d (W)		205 M 200[c] F			Dietz et al. 1992 Barium chloride	
41	Mouse (B6C3F1)	90 d (W)		450[c] M 495 F			NTP 1994 Barium chloride	Histological examination of reproductive tisses.

Table 3-1 Levels of Significant Exposure to Barium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
42	Mouse (B6C3F1)	15 d (W)		70[c] M 85 F			NTP 1994 Barium chloride	
Developmental								
43	Rat (Fischer- 344)	M: 60 d F: 30 d (W)		115 F	180 F (decreased pup body weight and nonsignificant decrease in litter size)		Dietz et al. 1992 Barium chloride	
44	Mouse (B6C3F1)	M: 60 d F: 30 d (W)		200 F			Dietz et al. 1992 Barium chloride	
CHRONIC EXPOSURE								
Death								
45	Mouse (B6C3F1)	2 yr (W)				160 M (increased mortality)	NTP 1994 Barium chloride	
Systemic								
46	Rat (Sprague-Dawley)	68 wk (W)	Resp	15 M			McCauley et al. 1985 NR	
			Cardio	15 M				
			Gastro	15 M				
			Musc/skel	15 M				
			Hepatic	15 M				
			Renal	15 M				
			Ocular	15 M				
			Bd Wt	15 M				

Table 3-1 Levels of Significant Exposure to Barium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
47	Rat (Fischer- 344)	2 yr (W)	Resp	60 M			NTP 1994 Barium chloride	
			Cardio	60 M				
			Gastro	60 M				
			Hemato	60 M				
			Musc/skel	60 M				
			Hepatic	60 M				
			Renal	60 M				
			Ocular	60 M				
			Bd Wt	60 M				
			Metab	60 M				
48	Rat (Long- Evans)	16 mo 7 d/wk (W)	Cardio	0.17 F	0.8 F (increased blood pressure)		Perry et al. 1983, 1985, 1989 Barium chloride	Animals were fed a low mineral diet.
					7.2 F (depressed rates of cardiac contraction and electrical conductivity)			

Table 3-1 Levels of Significant Exposure to Barium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
49	Mouse (B6C3F1)	2 yr (W)	Resp	160 M			NTP 1994 Barium chloride	
			Cardio	160 M				
			Gastro	160 M				
			Hemato	160 M				
			Musc/skel	160 M				
			Hepatic	160 M				
			Renal	75 M[d]		160 M (marked nephropathy)		
			Ocular	160 M				
			Bd Wt	75 M		160 M (weight loss)		
Immuno/ Lymphoret								
50	Rat (Sprague-Dawley)	68 wk (W)		15 M			McCauley et al. 1985 NR	Histological examination of thymus and lymph nodes.
51	Rat (Fischer- 344)	2 yr (W)		60 M			NTP 1994 Barium chloride	Histological examination of spleen and thymus.
52	Mouse (B6C3F1)	2 yr (W)		75 M	160 M (lymphoid depletion in the spleen and decreased relative and absolute spleen weight)		NTP 1994 Barium chloride	Histological examination of thymus and spleen.

Table 3-1 Levels of Significant Exposure to Barium - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Neurological								
53	Rat (Sprague-Dawley)	68 wk (W)		15 M			McCauley et al. 1985 NR	Histological examination of brain.
54	Rat (Fischer- 344)	2 yr (W)		60 M			NTP 1994 Barium chloride	Histological examination of brain.
55	Mouse (B6C3F1)	2 yr (W)		160 M			NTP 1994 Barium chloride	Histological examination of brain.
Reproductive								
56	Rat (Sprague-Dawley)	68 wk (W)		15 M			McCauley et al. 1985 NR	Histological examination of reproductive tissues.
57	Rat (Fischer- 344)	2 yr (W)		60[c] M 75 F			NTP 1994 Barium chloride	Histological examination of reproductive tissues.
58	Mouse (B6C3F1)	2 yr (W)		160[c] M 200 F			NTP 1994 Barium chloride	Histological examination of reproductive tissues.

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

b Used to derive an intermediate duration oral minimal risk level (MRL) of 0.2 mg barium/kg/day; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) and modifying factor of 3 to account for database deficiencies.

c Differences in levels of health effects and cancer effects between male and females are not indicated in Figure 3-1. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

d The chronic-duration oral MRL of 0.2 mg barium/kg/day was calculated using benchmark dose analysis. The BMDL5 of 61 mg barium/kg/day was divided by an uncertainty factor of 100 (10 to account for extrapolation from animals to humans and 10 for human variability) and modifying factor of 3 to account for database deficiencies.

Cardio = cardiovascular; d = day; F = female; Gastro = gastrointestinal; (GW) = gavage in water; Hemato = hematological; LD50 = lethal dose, 50% kill; M = male; mo = month; Musc/skel = musculoskeletal; NS = not specified; NR = not reported; Resp = respiratory; (W) = drinking water; wk = week; x = time(s); yr = year

Figure 3-1 Levels of Significant Exposure to Barium - Oral

Acute (≤14 days)

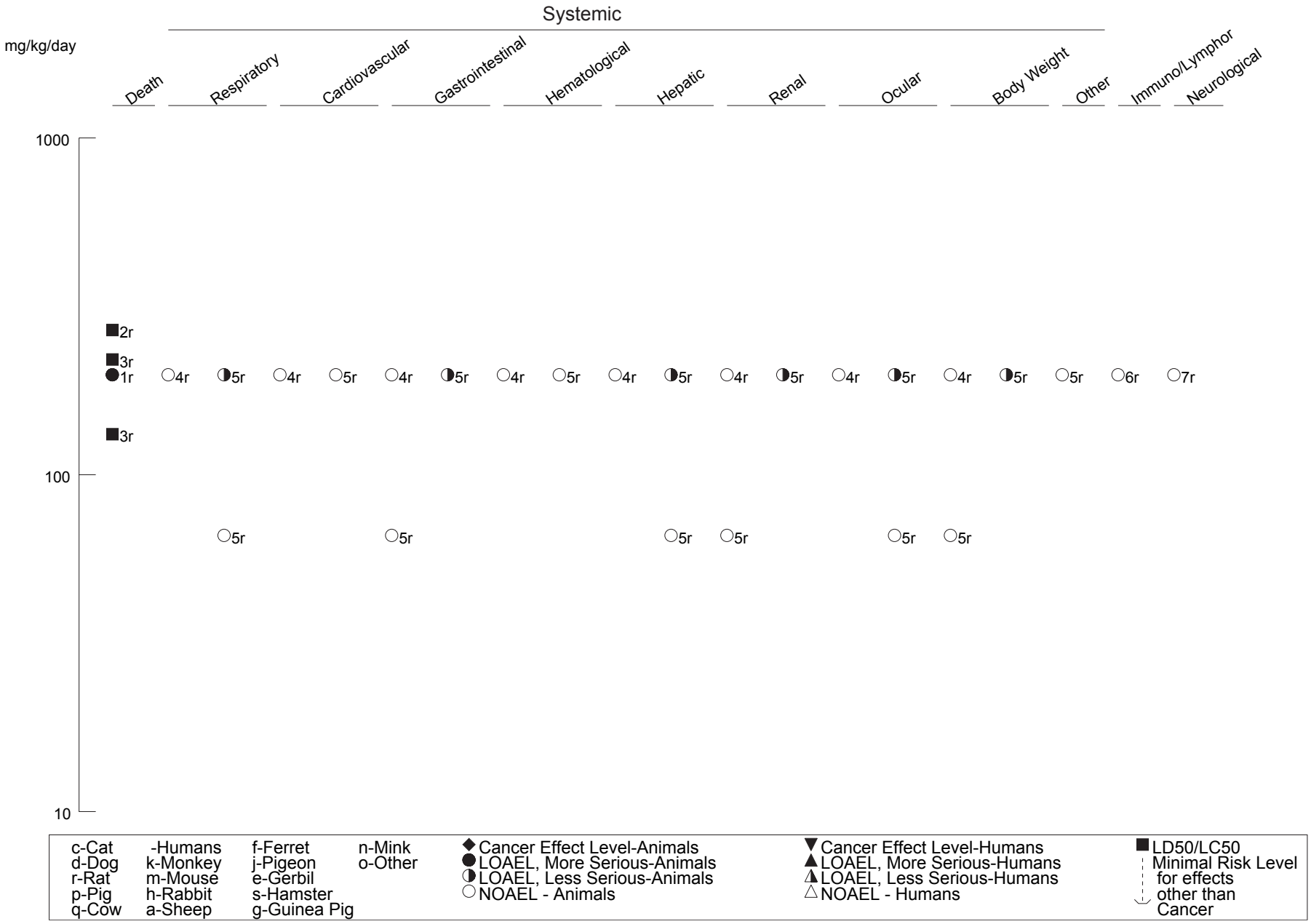
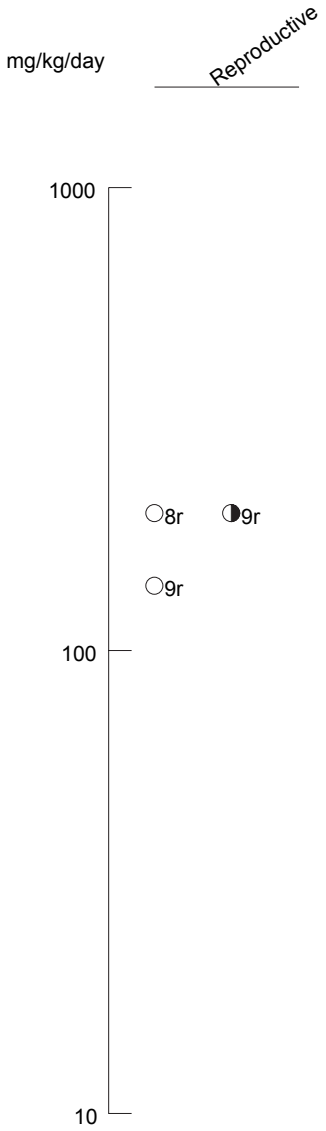


Figure 3-1 Levels of Significant Exposure to Barium - Oral *(Continued)*

Acute (≤14 days)



c-Cat -Humans f-Ferret n-Mink
d-Dog k-Monkey j-Pigeon o-Other
r-Rat m-Mouse e-Gerbil
p-Pig h-Rabbit s-Hamster
q-Cow a-Sheep g-Guinea Pig

◆ Cancer Effect Level-Animals
● LOAEL, More Serious-Animals
◑ LOAEL, Less Serious-Animals
○ NOAEL - Animals

▼ Cancer Effect Level-Humans
▲ LOAEL, More Serious-Humans
◭ LOAEL, Less Serious-Humans
△ NOAEL - Humans

■ LD50/LC50
Minimal Risk Level for effects other than Cancer

Figure 3-1 Levels of Significant Exposure to Barium - Oral *(Continued)*

Intermediate (15-364 days)

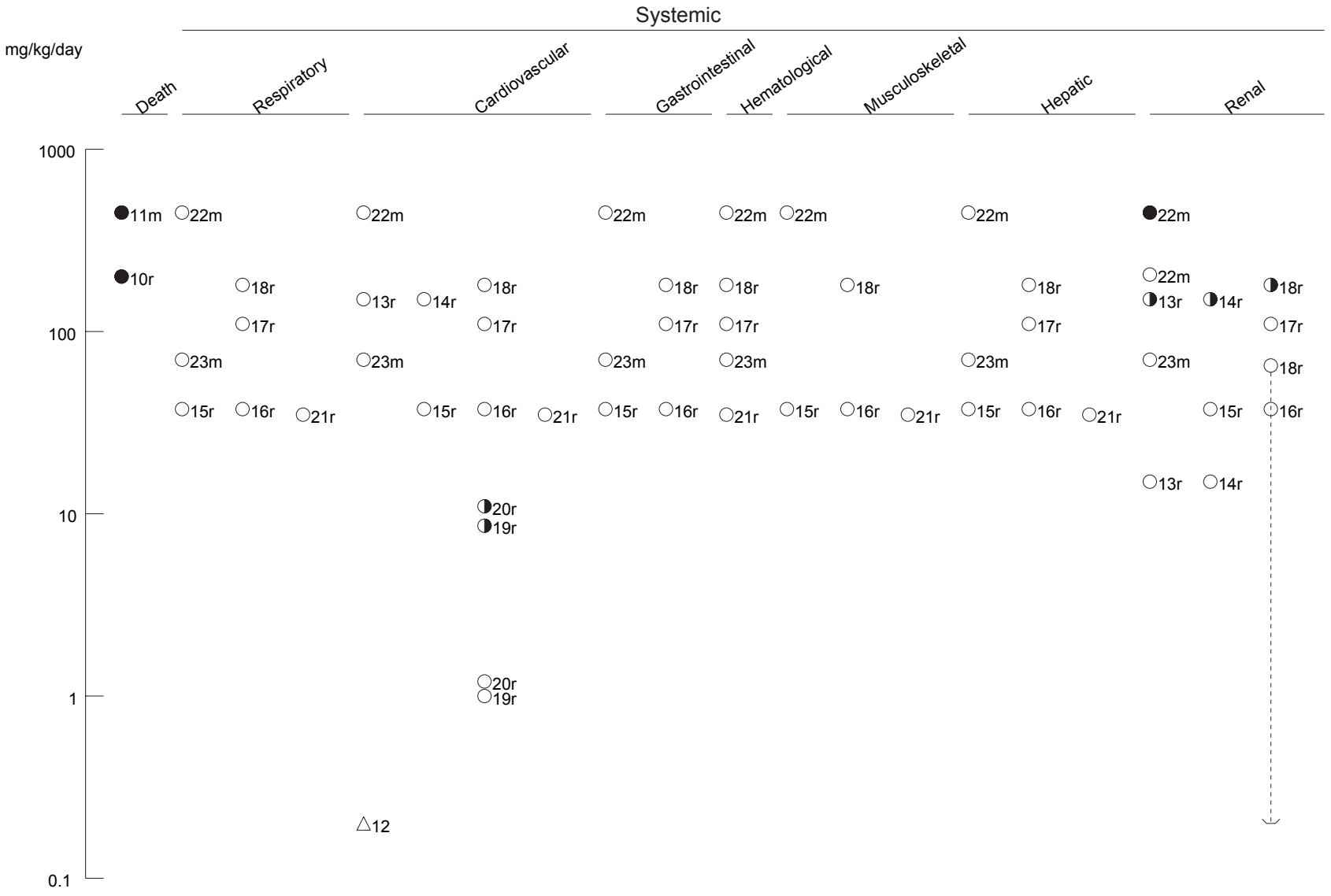


Figure 3-1 Levels of Significant Exposure to Barium - Oral *(Continued)*

Intermediate (15-364 days)

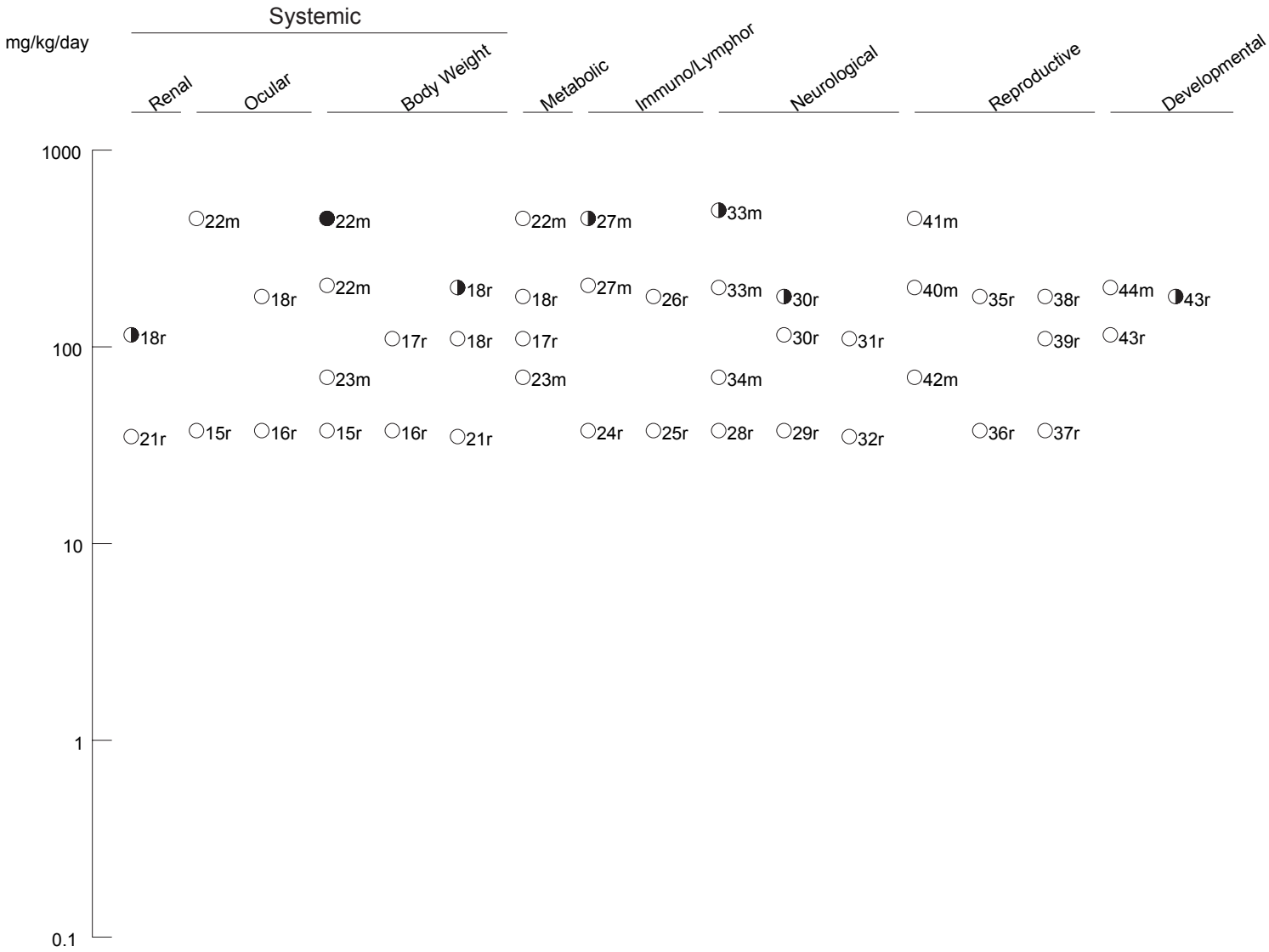
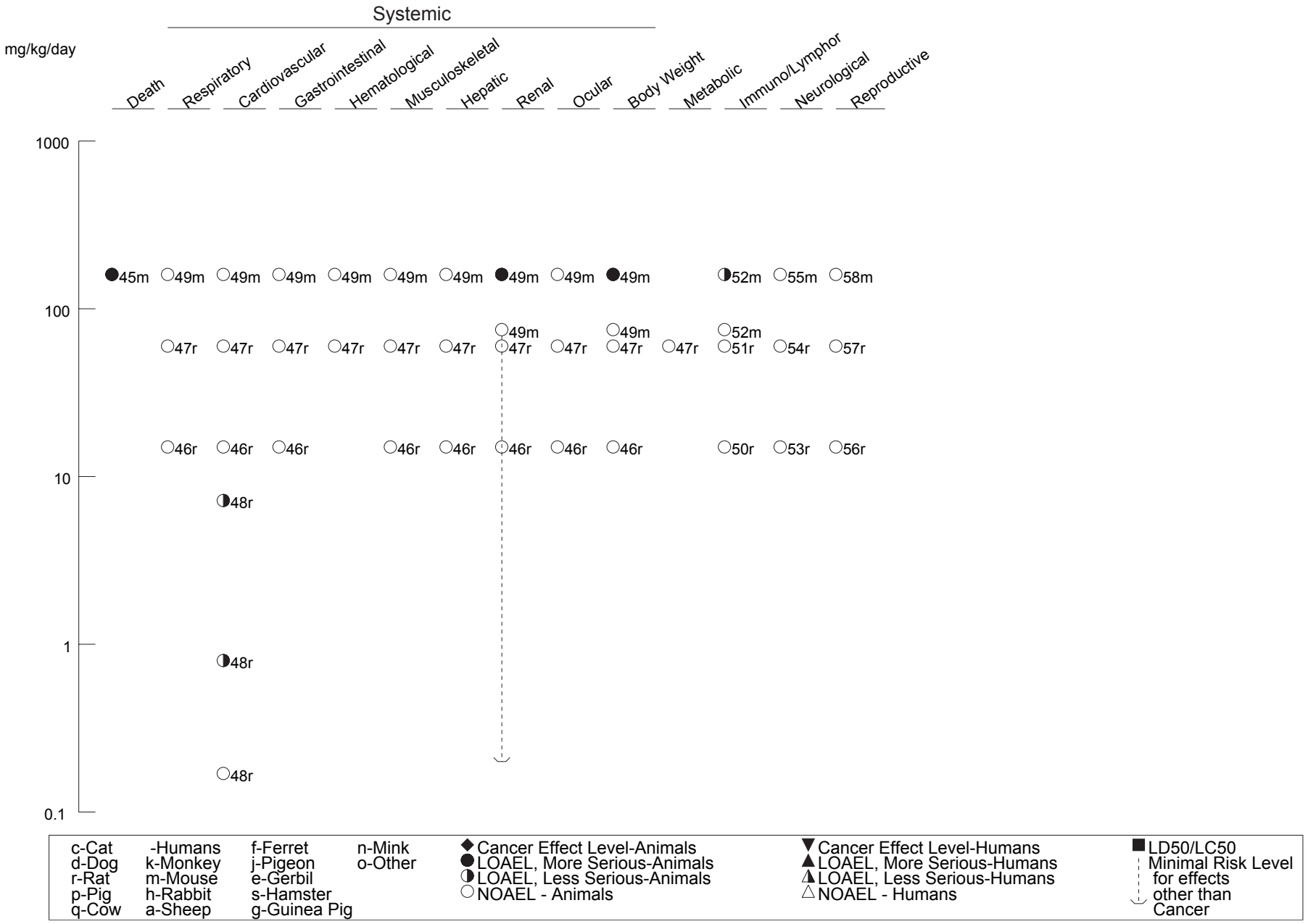


Figure 3-1 Levels of Significant Exposure to Barium - Oral *(Continued)*

Chronic (≥365 days)



alteration in blood pressure measurements or alterations in hypertension, heart disease, or stroke among residents of two communities with elevated (0.2 mg barium/kg/day) or low (0.003 mg barium/kg/day) levels of barium in drinking water (Brenniman and Levy 1985; Brenniman et al. 1979a, 1981). Interpretation of this study is limited by the lack of information on tap water consumption, and the fact that blood pressure was measured 3 times in a single 20-minute period and not repeatedly over a longer period, and the incidence of hypertension, stroke, and heart disease was taken from subject-completed questionnaires and not confirmed by testing or examination of medical records. Brenniman and associates (Brenniman and Levy 1985; Brenniman et al. 1979a, 1981) also conducted a mortality study of residents living in communities with elevated or low barium levels in drinking water. Significantly higher mortality rates for cardiovascular disease and heart disease (arteriosclerosis) were found in the elevated barium communities (0.06–0.3 mg barium/kg/day) than in the low barium communities (0.006 mg barium/kg/day). The largest difference between the groups was in individuals 65 years of age and older. These results should be interpreted cautiously because the study did not control for a number of potential confounding variables such as the use of water softeners, which would reduce the amount of barium and increase sodium levels, duration of exposure, or actual barium intakes.

Several animal studies have examined potential cardiovascular end points following acute-, intermediate-, or chronic-duration exposures. No histological alterations have been observed in the hearts of rats and mice exposed to barium chloride, barium acetate, or an unspecified barium compound for intermediate or chronic durations (Borzelleca et al. 1988; McCauley et al. 1985; NTP 1994; Perry et al. 1983, 1985, 1989; Schroeder and Mitchener 1975a; Tardiff et al. 1980). Significant increases in systolic blood pressure were observed in rats exposed to 8.6 or 11 mg barium/kg/day for 1 or 4 months, respectively; no effect levels were 1.0 and 1.2 mg barium/kg/day (Perry et al. 1983, 1985, 1989). When the duration of exposure was longer (8–16 months), the LOAEL for increased blood pressure was 0.80 mg barium/kg/day and the NOAEL was 0.17 mg barium/kg/day (Perry et al. 1983, 1985, 1989). Depressed rates of cardiac contraction and cardiac conductivity and decreased cardiac ATP levels were observed in another group of rats exposed to 7.2 mg barium/kg/day. In contrast to the findings in the Perry study (1983, 1985, 1989), no significant alterations in blood pressure were observed in rats exposed to up to 150 mg barium/kg/day in drinking water for 16 weeks (McCauley et al. 1985); it should be noted that the McCauley et al. (1985) studies were conducted in uninephrectomized rats or Dahl salt-sensitive and salt-resistant rats. NTP (1994) also found no significant alterations in blood pressure, heart rate, or ECG readings in rats exposed to 180 mg barium/kg/day for 45 or 90 days. The low metal diet used in the Perry et al. (1983, 1985, 1989) study may have influenced the study outcome.

Gastrointestinal Effects. All cases of acute oral barium poisoning in adults exhibit gastrointestinal disturbances as the initial symptoms. These include gastric pain, vomiting, and diarrhea (Das and Singh 1970; Diengott et al. 1964; Downs et al. 1995; Gould et al. 1973; Jha et al. 1993; Lewi and Bar-Khayim 1964; McNally 1925; Morton 1945; Ogen et al. 1967; Phelan et al. 1984; Silva 2003; Talwar and Sharma 1979; Wetherill et al. 1981). In one case, severe gastrointestinal hemorrhage occurred in an adult male victim (Diengott et al. 1964).

Although gastrointestinal effects have been observed in some animal studies, most studies have not found effects. Inflammation of the intestines was noted in rats receiving a single gavage dose of 198 mg barium/kg as barium chloride (Borzelleca et al. 1988); but not in rats administered 10 doses of 198 mg barium/kg/day (Borzelleca et al. 1988). Stomach rupture, bowel obstruction, and gastrointestinal hemorrhage have been observed in rats dosed with barium sulfate; however, those adverse effects were most likely due to the massive doses of barium sulfate used in the study (25–40% of body weight) and not necessarily to barium toxicity (Boyd and Abel 1966). A 15-day exposure of male and female rats and mice to 110 or 70 mg barium/kg/day as barium chloride in drinking water, respectively, did not result in histological alterations in the gastrointestinal tract (NTP 1994). No gross or microscopic lesions of the esophagus, stomach, pancreas, small intestines, or colon were noted in several intermediate and chronic experiments in which male and female rats were exposed to doses as high as 180 mg barium/kg/day as an unspecified barium compound or barium chloride in drinking water (McCauley et al. 1985; NTP 1994) or male and female mice exposed to doses as high as 450 mg barium/kg/day as barium chloride (NTP 1994).

Hematological Effects. Results of animal studies indicate that acute, intermediate, and chronic oral exposure to barium is not associated with any adverse hematological effects. No alterations were found in rats administered 198 mg barium/kg/day as barium chloride for 10 days (Borzelleca et al. 1988) or in rats or mice exposed to 110 or 70 mg/kg/day, respectively, as barium chloride in drinking water for 15 days (NTP 1994). Intermediate and chronic oral exposure of rats to barium acetate and barium chloride in drinking water has not been associated with any significant or treatment-related changes in a variety of hematological parameters (NTP 1994; Tardiff et al. 1980). Elemental barium doses in these intermediate and chronic drinking water studies ranged from 15 to 450 mg/kg/day.

Musculoskeletal Effects. The predominant musculoskeletal effect observed in cases of barium toxicity in humans is progressive muscle weakness, often leading to partial or total paralysis (Das and Singh 1970; Diengott et al. 1964; Gould et al. 1973; Lewi and Bar-Khayim 1964; McNally 1925; Morton 1945; Ogen et al. 1967; Phelan et al. 1984; Wetherill et al. 1981). In severe cases, the paralysis affects

the respiratory system (Das and Singh 1970; Gould et al. 1973; Lewi and Bar-Khayim 1964; Morton 1945; Ogen et al. 1967; Phelan et al. 1984; Wetherill et al. 1981). The likely cause of the muscle weakness was the barium-induced hypokalemia rather than a direct effect on muscles.

Very limited animal data are available regarding the musculoskeletal effects of barium following oral exposure. No gross and microscopic lesions were observed in skeletal system of several intermediate and chronic experiments in which rats were exposed to an unspecified barium compound or barium chloride in drinking water at doses as high as 180 mg barium/kg/day for intermediate duration and as high as 60 mg barium/kg/day for chronic duration (McCauley et al. 1985; NTP 1994; Tardiff et al. 1980); similarly, no effects were observed in mice exposed to 450 or 160 mg barium/kg/day as barium chloride in drinking water for intermediate or chronic durations, respectively (NTP 1994).

Hepatic Effects. In one case study involving accidental acute ingestion of barium carbonate in an adult female, some degeneration of the liver was noted post-mortem (McNally 1925). Adverse hepatic effects in animals following oral barium exposure have been minor or have not been observed. Decreased liver/brain weight ratio and darkened liver were observed in rats administered a single gavage dose of 198 mg barium/kg as barium chloride; however, these changes were not associated with any microscopic hepatic lesions or alterations in serum enzymes (e.g., serum glutamic-oxaloacetic transaminase [SGOT], serum glutamic pyruvic transaminase [SGPT], alkaline phosphatase). No histological or liver weight alterations were observed in rats dosed with 198 mg barium/kg/day as barium chloride for 1 or 10 days (Borzelleca et al. 1988) or in rats and mice exposed to 110 or 70 mg barium/kg/day, respectively, as barium chloride in drinking water for 15 days (NTP 1994). Intermediate and chronic studies involving oral exposure of rats or mice to barium in drinking water did not find significant alterations in liver weight or liver histopathology following exposure to doses as high as 180 mg barium/kg/day for rats and 450 mg barium/kg/day for mice (McCauley et al. 1985; NTP 1994; Schroeder and Mitchener 1975a, 1975b; Tardiff et al. 1980).

Renal Effects. Toxic effects on the kidneys have been observed in several adult cases of acute barium poisoning. Effects include hemoglobin in the urine (Gould et al. 1973) (which may be indicative of kidney damage), renal insufficiency (Lewi and Bar-Khayim 1964; Phelan et al. 1984), degeneration of the kidneys (McNally 1925), and acute renal failure (Wetherill et al. 1981).

Studies in animals suggest that the kidney is a critical target of barium toxicity. An increase in relative kidney weight (kidney/brain weight ratio) was observed in male and female rats receiving a single gavage

dose of 198 mg barium/kg/day as barium chloride in water (Borzelleca et al. 1988). Increases in relative kidney weight (kidney to brain weight ratio) were also observed in female rats receiving gavage doses of 66, 96, or 138 mg barium/kg/day as barium chloride in water for 10 days, but not at 198 mg barium/kg/day (Borzelleca et al. 1988). Significant reductions in blood urea nitrogen (BUN) were also observed in females exposed to 66–198 mg barium/kg/day and in males exposed to 198 mg barium/kg/day. The changes in BUN levels were not considered to be biologically significant because BUN levels are typically increased in response to kidney damage, the magnitude of change was slight (less than 15%), and there were no differences between the barium-exposed groups. The changes in relative kidney weights or BUN levels were not associated with gross or microscopic renal lesions. Studies of rats and mice did not find significant alterations in kidney weights or the incidence of renal lesions following a 15-day exposure to 110 or 70 mg barium/kg/day, respectively, as barium chloride in drinking water (NTP 1994).

Exposure of rats to doses as high as 65 mg barium/kg/day for an intermediate duration did not result in any alterations in kidney weight or the occurrence of histopathological lesions (McCauley et al. 1985; NTP 1994; Tardiff et al. 1980). At 115 mg barium/kg/day, significant increases in absolute and relative kidney weights were observed in female rats (NTP 1994). Electron microscopy detected glomerular lesions consisting of fused podocyte processes and thickening of the capillary basement membrane in rats exposed to 150 mg barium/kg/day (McCauley et al. 1985). At slightly higher doses (180 mg barium/kg/day), minimal to mild dilatation of the proximal convoluted tubules of the outer medulla and renal cortex was observed in male and female rats (NTP 1994). In mice, nephropathy characterized by mild to moderate tubule dilatation, regeneration, and atrophy was observed in males and females exposed to 450 mg barium/kg/day as barium chloride, but not to 205 mg barium/kg/day (NTP 1994).

Three chronic-duration studies assessed the renal toxicity of barium. No adverse effects were observed in rats exposed via drinking water to 15 mg barium/kg/day of an unspecified barium compound for 68 weeks (McCauley et al. 1985), 60 mg barium/kg/day as barium chloride for 2 years (NTP 1994), or lifetime exposure to 0.7 mg barium/kg/day as barium acetate (Schroeder and Mitchener 1975a). In mice, exposure to 160–200 mg barium/kg/day resulted in moderate to marked nephropathy, characterized by extensive regeneration of cortical and medullary tubule epithelium, tubule dilatation, hyaline cast formation, interstitial fibrosis, and glomerulosclerosis (NTP 1994); at the next lowest dose tested (75 mg barium/kg/day), the incidence of nephropathy did not differ from controls. No kidney lesions were observed in mice following lifetime exposure to 0.95 mg barium/kg/day as barium acetate (Schroeder and Mitchener 1975b).

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

Ocular Effects. No studies were located regarding ocular effects in humans after oral exposure to barium. In studies with Sprague-Dawley rats, ocular discharge following administration of a single gavage dose of 198 mg barium/kg/day as barium chloride (Borzelleca et al. 1988); this was not reported in rats dosed for 10 days (Borzelleca et al. 1988). A nonsignificant increase in retinal dystrophy was observed in rats following intermediate and chronic oral exposure to 12–37.5 mg barium/kg/day as an unspecified barium compound (McCauley et al. 1985). Although the retinal dystrophy was statistically insignificant, a dose-related trend was observed if different duration exposure groups were combined (McCauley et al. 1985). Both ocular discharge and retinal dystrophy are commonly observed in Sprague-Dawley rats; consequently, the ocular lesions noted in these animal studies cannot necessarily be attributed to oral barium exposure. Ocular lesions were not observed in F344 rats or B6C3F1 mice exposed to barium chloride in drinking water for 90 days or 2 years to doses as high as 180 mg barium/kg/day in rats and 450 mg barium/kg/day in mice (NTP 1994).

Body Weight Effects. Body weight has been monitored in a number of acute, intermediate, and chronic studies in which rats and mice were exposed orally to barium compounds (Borzelleca et al. 1988; McCauley et al. 1985; NTP 1994; Perry et al. 1983, 1985, 1989; Schroeder and Mitchener 1975a, 1975b; Tardiff et al. 1980). In general, body weight effects have only been observed at lethal doses. A decrease in body weight was observed in rats receiving a single gavage dose of 198 mg barium/kg/day as barium chloride (Borzelleca et al. 1988), in rats exposed to 200 mg barium/kg/day as barium chloride in drinking water for an intermediate duration (NTP 1994), and in mice exposed to 450 or 160 mg barium/kg/day as barium chloride in drinking water for intermediate and chronic durations, respectively (NTP 1994).

Metabolic Effects. Hypokalemia is a common finding in cases of severe barium poisoning (Deng et al. 1991; Diengott et al. 1964; Downs et al. 1995; Gould et al. 1973; Jha et al. 1993; Koch et al. 2003; Lewi and Bar-Khayim 1964; Phelan et al. 1984; Talwar and Sharma 1979; Wetherill et al. 1981). In a group of cases examined by Deng et al. (1991), serum potassium levels ranged from 0.8 to 2.7 mEq/L; normal values range from 3.5 to 5 mEq/L. Alterations in serum potassium levels have not been reported in rats exposed to 110 or 180 mg barium/kg/day as barium chloride in drinking water for 15 or 90 days,, respectively (NTP 1994).

3.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans after oral exposure to barium. Several animal studies have examined potential lymphoreticular effects, particularly damage to the thymus, spleen, and lymph nodes. Acute gavage exposure of rats to doses as high as 198 mg barium/kg/day as barium chloride for 1 or 10 days was not associated with any changes in thymus weight or any gross lesions of the thymus (Borzelleca et al. 1988). Intermediate and chronic oral exposure of rats to nominal concentrations of barium in drinking water of 37.5 and 15 mg/kg/day, respectively, of an unspecified barium compound was not associated with lesions of the lymph nodes or thymus upon gross and histopathologic examination (McCauley et al. 1985). No histopathological alterations were observed in the spleen or thymus of rats exposed to 180 or 60 mg barium/kg/day for an intermediate or chronic duration, respectively (NTP 1994). In mice, thymic and splenic atrophy were observed at 450 mg barium/kg/day after intermediate exposure and lymphoid depletion in the spleen and decreased spleen weight were observed at 160 mg barium/kg/day after chronic exposure (NTP 1994). These effects were probably secondary to the severe nephropathy and weight loss observed at these doses.

No studies have assessed the potential of barium to impair immune function.

The highest NOAEL values for lymphoreticular effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.4 Neurological Effects

Numbness and tingling around the mouth and neck were sometimes among the first symptoms of barium toxicity in humans (Lewi and Bar-Khayim 1964; Morton 1945). Occasionally, these neurological symptoms extended to the extremities (Das and Singh 1970; Lewi and Bar-Khayim 1964). Partial and complete paralysis occurred in severe cases, often accompanied by an absence of deep tendon reflexes (Das and Singh 1970; Diengott et al. 1964; Gould et al. 1973; Lewi and Bar-Khayim 1964; Morton 1945; Ogen et al. 1967; Phelan et al. 1984; Wetherill et al. 1981). Post-mortem examination in one case of poisoning by ingestion of barium sulfide revealed brain congestion and edema (McNally 1925).

Animal studies have not found significant alterations in brain weight or histopathology following acute gavage exposure of rats for 1 or 10 days to doses as high as 198 mg barium/kg/day as barium chloride (Borzelleca et al. 1988), intermediate oral exposure of rats to doses as high as 115 mg barium/kg/day in drinking water (McCauley et al. 1985; NTP 1994; Tardiff et al. 1980), intermediate-duration exposure of

mice to doses less than 450 mg barium/kg/day as barium chloride in drinking water (NTP 1994), or chronic exposure of rats and mice to doses greater than 60 or 160 mg barium/kg/day as barium chloride in drinking water, respectively (NTP 1994). Neurobehavioral performance (spontaneous motor activity, grip strength, tail flick latency, startle response, hindlimb foot splay) was evaluated in rats and mice exposed to barium chloride for 15 or 90 days (NTP 1994). No alterations were observed in rats or mice following a 15-day exposure to 110 or 70 mg barium/kg/day. Slight decreases in motor activity were observed in rats exposed to 10–115 mg barium/kg/day for 90 days; these changes were not considered to be biologically significant. However, in female rats exposed to 180 mg barium/kg/day, spontaneous motor activity was 30% lower than controls; this difference was considered to be biologically significant. In mice, the only alteration noted was a decrease in forelimb grip strength in females exposed to 495 mg barium/kg/day for 90 days; the investigators noted that this may have been due to debilitation. The highest NOAEL values and reliable LOAEL values for neurological effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to barium. However, limited data are available from acute, intermediate, and chronic animal studies in which certain reproductive organs were weighed and examined grossly and microscopically following oral barium exposure. Gavage exposure of rats to doses of 198 mg barium/kg/day as barium chloride for 10 days resulted in decreased ovary weight and decreased ovary/brain weight ratio (Borzelleca et al. 1988); no alterations were observed after a single gavage dose with 198 mg barium/kg/day (Borzelleca et al. 1988). Neither study found changes in testicular weight, and no gross lesions of the ovaries or testes were observed at this dose. No histological alterations were observed in the reproductive tissues of male and female rats and mice exposed to 110 mg barium/kg/day (rats) or 70/85 mg barium/kg/day (mice) as barium chloride in drinking water (NTP 1994). Intermediate and chronic oral exposure of rats to barium in drinking water at doses of 200 mg barium/kg/day and lower was not associated with any gross or histopathologic lesions of the uterus, ovaries, or testes (Dietz et al. 1992; McCauley et al. 1985; NTP 1994). Similarly, no histopathological alterations were observed in reproductive tissues of mice exposed to 495 mg barium/kg/day and lower for an intermediate duration (NTP 1994) or 160 mg barium/kg/day or lower for a chronic duration (NTP 1994). Additionally, no alterations in epididymal sperm counts, sperm motility, or sperm morphology were observed in rats or mice exposed to 200 or 205 mg barium/kg/day, respectively, as barium chloride in drinking water for 60 days (Dietz et al. 1992).

There are limited data on the potential of barium to impair reproductive function. No significant alterations in pregnancy rate or gestation length were observed in rats or mice exposed to approximately 200 mg barium/kg/day as barium chloride in drinking water (Dietz et al. 1992); the males were exposed for 60 days prior to mating and the females were exposed for 30 days.

The highest NOAEL values and all reliable LOAEL values for reproductive effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.6 Developmental Effects

Studies regarding developmental effects of barium following oral exposure are limited to one human study (Morton et al. 1976) and three animal studies (Dietz et al. 1992; Tarasenko et al. 1977). A statistically significant negative correlation was found between barium concentrations in drinking water and human congenital malformation rates of the central nervous system in South Wales (Morton et al. 1976). A negative correlation implies that as the barium concentration in drinking water increased, the rate of central nervous system malformations decreased. This statistical study is of limited value in identifying a NOAEL for developmental effects because exposure conditions (duration and frequency of exposure, dose, number of subjects exposed) were not characterized.

Developmental effects were reported in a study in which an unspecified animal species was orally administered a dose of barium carbonate that was equal to 1/16 of the LD_{50} for 24 days prior to conception and pregnancy (Tarasenko et al. 1977). Reported effects in offspring included increased mortality during the first 2 months, increased leukocyte count, disturbances in liver function, and increased urinary excretion of hippuric acid. This study is inadequate for evaluating developmental effects of oral barium exposure because of major study limitations. These limitations include a general lack of information provided by the authors regarding experimental methods, exposure conditions, and test results, and no information as to the species and number of animals tested, the purity of the test material, the statistical methods used, and whether or not controls were used.

In studies by Dietz et al. (1992), male rats and mice were exposed to barium chloride in drinking water for 60 days and mated to females exposed to barium chloride for 30 days. In the rats, exposure to 180/200 mg barium/kg/day resulted in significant decreases in pup birth weights. Decreases in the live litter size at postnatal days 0 and 5 were also observed in the 180/200 mg barium/kg/day group, but the difference was not statistically significant; litter sizes were 9.0 and 9.3 pups in controls on days 0 and 5,

and 7.2 and 7.1 pups on days 0 and 5 in the 200 mg barium/kg/day group. No adverse developmental effects were observed in the mice (highest dose tested was 200 mg barium/kg/day).

The highest NOAEL values and all reliable LOAEL values for developmental effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.7 Cancer

No studies were located regarding cancer in humans after oral exposure to barium. Several animal studies evaluated the induction of tumors following chronic oral exposure to barium (NTP 1994; Schroeder and Mitchener 1975a, 1975b). In studies by Schroeder and Mitchener (1975a, 1975b), rats and mice were exposed to 0.7 and 0.95 mg barium/kg/day, respectively, as barium acetate in drinking water for lifetime. No differences in the incidence of tumors were noted between treated animals and vehicle controls in either study. These studies are inadequate for evaluating the carcinogenic potential of barium because insufficient numbers of animals were used for a carcinogenicity study, it was not determined whether or not a maximum tolerated dose was achieved, a complete histological examination was not performed, the purity of the test material was not specified, and only one exposure dose was used in each study. Studies conducted by the NTP (1994) are considered adequate for carcinogenicity assessment. In rats exposed to doses as high as 60–75 mg barium/kg/day as barium chloride in drinking water, significant negative trends for mononuclear cell leukemia, adrenal medulla pheochromocytoma, and mammary gland neoplasms were found. No significant increases in malignant tumors were observed. Similarly, no increases in malignant tumor incidences were observed in mice chronically exposed to doses up to 160–200 mg barium/kg/day as barium chloride in drinking water.

3.2.3 Dermal Exposure

Limited information is available regarding the health effects of barium following dermal exposure. Barium salts would be expected to have a local effect on skin surfaces and would not likely be absorbed systematically to any great extent. Available studies include a case report of an individual exposed dermally to molten barium chloride (Stewart and Hummel 1984), a skin irritation study evaluating barium carbonate in experimental animals (Tarasenko et al. 1977), and a skin-painting study in which mice were exposed dermally to a barium hydroxide extract of tobacco leaf (Van Duuren et al. 1968). No reliable information was available from any of these dermal studies to identify study NOAELs or LOAELs for barium. In the case report (Stewart and Hummel 1984), the dermal burns that developed in the individual

exposed to molten barium chloride may potentially have contributed to some of the reported health effects, which are described briefly in Section 3.2.3.2 (Systemic Effects).

3.2.3.1 Death

No studies were located regarding death in humans or animals after dermal exposure to barium.

3.2.3.2 Systemic Effects

No studies were located regarding respiratory, hematological, musculoskeletal, hepatic, renal, endocrine, or body weight effects in humans or animals after dermal exposure to barium.

Cardiovascular Effects. An abnormal electrocardiogram was observed in a 62-year-old man burned by molten barium chloride (Stewart and Hummel 1984). No studies were located regarding cardiovascular effects in animals after dermal exposure to barium.

Gastrointestinal Effects. A 62-year-old man experienced vomiting after he was accidentally burned by molten barium chloride (Stewart and Hummel 1984). No studies were located regarding gastrointestinal effects in animals after dermal exposure to barium.

Dermal Effects. Molten barium chloride induced burns on the skin of a 62-year-old man who was accidentally exposed through an explosion. The dermal burns, however, were very probably due to the molten nature of the material and not necessarily to barium chloride (Stewart and Hummel 1984).

The dermal effects of barium carbonate were examined in a study with rats and rabbits (Tarasenko et al. 1977). When barium carbonate in lanolin was applied to the skin, ulcers developed. These dermal lesions reportedly disappeared within a month when dermal treatment was discontinued. Although these findings suggest that barium carbonate may be a dermal irritant, these particular investigations are inadequate for establishing the dermal effects of barium because of a number of significant study limitations. The authors provided few details regarding experimental methods and results, and no information as to the concentration of barium carbonate used, the number of animals used, and whether or not controls were used.

Ocular Effects. Information on the ocular toxicity of barium is limited to a study conducted by Tarasenko et al. (1977) in rats and rabbits. When barium carbonate powder was introduced into the

conjunctival sac, purulent discharge, conjunctivitis, and slight opacity of the cornea developed. As noted in the Dermal Effects section, interpretation of these results is limited by the poor reporting of study methods and results, lack of information on barium carbonate concentration, and whether controls were used.

Metabolic Effects. A 62-year-old victim accidentally exposed to molten barium chloride had a depressed plasma potassium level when admitted to the hospital (Stewart and Hummel 1984).

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

3.2.3.3 Immunological and Lymphoreticular Effects

3.2.3.4 Neurological Effects

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

No studies were located regarding cancer in humans after dermal exposure to barium. Dysplasia of the cervical epithelium was reportedly induced in a woman who had a barium chloride solution applied to her cervix (Ayre 1966). The use of dimethyl sulfoxide in combination with the barium chloride solution reportedly enhanced the ability of barium chloride to induce dysplasia. Dysplasia can be regarded as a potential precancerous lesion. The significance of the observations reported in this study are difficult to assess, since only one subject was exposed and because there have been no reports of similar findings in other human or animal studies. Also, the vehicle used was not specified in this study.

No studies were located regarding cancer in animals after dermal exposure to barium. However, results of one skin-painting study with mice suggest that barium hydroxide extract derived from tobacco leaf may act as a tumor-promoting agent (Van Duuren et al. 1968); the purity of the barium hydroxide extract was not reported. In this study, mice were treated dermally for an unspecified period of time with either barium hydroxide extract alone, 7,12-dimethylbenz(a)anthracene (DMBA) alone (an initiating agent), or a combination of DMBA and barium hydroxide extract. After 1 year, none of the mice treated with barium hydroxide extract developed skin tumors. However, 3 out of 20 mice treated with DMBA alone and 7 out of 20 mice treated with a combination of both barium hydroxide extract and DMBA developed skin

papillomas and carcinomas. These results provide limited, but suggestive evidence that barium hydroxide extract of tobacco leaf acted as a tumor-promoting agent. However, it can not be determined whether or not this apparent positive tumorigenic response was due to barium hydroxide or some other component of the barium hydroxide tobacco leaf extract.

3.3 GENOTOXICITY

In vivo studies of barium genotoxicity are limited to a study in *Drosophila melanogaster*. In this study, positive results were found in the somatic mutation and recombination test when high levels of barium nitrate were used; the results were inconclusive at low barium nitrate levels (Yesilada 2001). *In vitro* studies were limited and summarized in Table 3-2. No significant alterations in gene mutation frequency were observed in *Salmonella typhimurium* (Monaco et al. 1990, 1991; NTP 1994) or *Escherichia coli* (Rossman et al. 1991). Similarly, barium chloride or barium nitrate did not result in deoxyribonucleic acid (DNA) damage in *Bacillus subtilis* (Kanematsu et al. 1980; Nishioka 1975). Tests of the fidelity of DNA synthesis using an avian myeloblastosis virus (AMV) DNA polymerase system showed that neither barium acetate nor barium chloride affect the accuracy of DNA replication (Sirover and Loeb 1976a, 1976b). However, studies with a DNA polymerase I system from *Micrococcus luteus*, demonstrated that concentrations of barium ion ≤0.1 mM stimulated DNA polymerase activity while concentrations greater than this inhibited polymerase activity (Korman et al. 1978). The significance of the inhibitory and stimulatory effects has not been determined. Results from an experiment designed to test the effect of barium chloride on sporulation frequency, recombination frequency, and meiotic failures in *Saccharomyces cerevisiae* demonstrated a definite inhibition of sporulation. Effects on recombination frequency and meiotic failures were ambiguous. Barium chloride may have caused a marginal increase in recombination frequency and information of diploid clones (Sora et al. 1986), but the data are inconclusive. In mammalian test systems, barium chloride did not increase the frequency of sister chromatid exchange or chromosome aberrations in Chinese hamster cells (NTP 1994). However, an increase in gene mutations was observed at the TK locus of L5178Y mouse lymphoma cells in the presence of metabolic activation, but not without metabolic activation (NTP 1994).

Table 3-2. Genotoxicity of Barium and Barium Compounds *In Vitro*

Species (test system)	End point	Results	Reference	Compound
Prokaryotic organisms:				
Salmonella typhimurium	Gene mutation frequency (with or without S9 activation)	–	Monaco et al. 1990, 1991; NTP 1994	Barium chloride
Escherichia coli WP2s(λ)	Gene mutation frequency	–	Rossman et al. 1991	Barium chloride
Bacillus subtilis	DNA damage (rec assay)	–	Kanematsu et al. 1980; Nishioka 1975	Barium chloride, barium nitrate
Eukaryotic organisms:				
Fungi				
Saccharomyces cerevesiae	Meiosis	–	Sora et al. 1986	Barium chloride
Avian myeloblastosis virus DNA polymerase	DNA synthesis	–	Sirover and Loeb 1976a, 1976b	Barium chloride, barium acetate
Mammalian cells:				
CHO cells	Sister chromatid exchange (with or without S9 activation)	–	NTP 1994	Barium chloride
CHO cells	Chromosome aberration (with or without S9 activation)	–	NTP 1994	Barium chloride
Mouse lymphoma cells	Gene mutation at TK locus With S9 activation Without S9 activation	 + –	NTP 1994	Barium chloride

– = negative result; + = positive result; CHO = Chinese hamster ovary

3.4 TOXICOKINETICS

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

No studies were located regarding absorption of barium in humans following inhalation exposure. Several animal studies have investigated the absorption of barium chloride or barium sulfate following inhalation, intratracheal injection, or nasal deposition. The results of these studies suggest that the rate and extent of absorption of barium from the respiratory tract depend on the exposure level, how much barium reaches the alveolar spaces, the clearance rate from the upper respiratory tract, and the solubility of the particular form of barium that was administered. Approximately 50–75% of inhaled barium chloride or barium sulfate is absorbed from the respiratory tract (Cuddihy and Griffith 1972; Morrow et al. 1968); approximately 65% of the barium chloride deposited in the nose is absorbed (Cuddihy and Ozog 1973b). Most of the barium absorption occurs within the first 24 hours (Cuddihy and Griffith 1972; Cuddihy et al. 1974). Barium chloride appears to be more rapidly absorbed than barium sulfate (Cuddihy et al. 1974), although the differences in particle size (AMADs of 2.3 and 1.0 μm for barium chloride and barium sulfate, respectively) may have influenced the absorption rate. In contrast to the rapid absorption of barium following inhalation or nasal deposition, most of the barium sulfate that is injected directly into the trachea of rats can be taken up into the epithelium membranes and remains in these membranes for at least a few weeks (Gore and Patrick 1982; Takahashi and Patrick 1987), suggesting that clearance in the upper respiratory tract is more efficient than in the trachea. Following intratracheal injection, the clearance of barium sulfate from the lungs was independent of lung burden over the range of 23.3–2,330 μg (Cember et al. 1961); this is consistent with the lack of evidence of lung overload following intermediate-duration inhalation exposure to 37.5 or 75 mg/m^3 barium sulfate (MMAD 4.3 μm, σg 1.7) (Cullen et al. 2000). Species differences in the retention of intratracheally administered radiolabelled (^{133}Ba) barium sulfate have been found. The percentages of ^{133}Ba retained in the trachea 1 week after administration were 0.41, 0.145, 0.044, and 0.043% in rats, rabbits, dogs, and monkeys, respectively (Takahashi and Patrick 1987; Takahashi et al. 1993).

3.4.1.2 Oral Exposure

The absorption of barium from the gastrointestinal tract is compound dependent. Barium sulfate is extremely insoluble and very little, if any, ingested barium sulfate is absorbed. Acid-soluble barium compounds, such as barium chloride and barium carbonate, are absorbed through the gastrointestinal

tract, although the amount of barium absorbed is highly variable. Older human studies estimated that barium was poorly absorbed; approximately 1–15% of the ingested dose was estimated to be absorbed (Harrision et al. 1956; LeRoy et al. 1966; Schroeder et al. 1972; Tipton et al. 1969). A re-examination of the methods used in these studies found a number of flaws; Leggett (1992) estimated that barium absorption in these studies was approximately 3–60%. Studies in adult rats and dogs estimated fractional absorption at 7% (Cuddihy and Griffith 1972; Taylor et al. 1962). Several unpublished animal studies discussed by Leggett (1992) found absorption rates of 1–50%. Experiments in rats have shown that younger animals (22 days old or less) absorb about 10 times more barium chloride from the gastrointestinal tract (63–84%) than do older animals (about 7%) (Taylor et al. 1962). Absorption was higher in fasted adult rats (20%) as compared to fed rats (7%). The International Commission for Radiation Protection (ICRP) estimates that the gastrointestinal absorption of barium is 20% in adults, 30% for children aged 1–15 years, and 60% in infants (ICRP 1993).

3.4.1.3 Dermal Exposure

No studies were located regarding absorption of barium in humans after dermal exposure. One animal study showed that barium applied to the skin of piglets was found in the various layers of the skin (Shvydko et al. 1971). Barium is not expected to cross the intact skin because of the high polarity of the forms in which it is most commonly encountered.

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

Shortly after dogs were exposed to radiolabelled (^{140}Ba) barium chloride, elevated activity was found in the upper respiratory tract, stomach, and small intestine (30% of initial burden), lungs and tracheobronchial tissue (6%), and various internal organs (64%) (Cuddihy and Griffith 1972). One day post-exposure, 44% of the label was detected in the skeleton, 1% in blood, and 4% in muscle; 26% of the dose was excreted.

3.4.2.2 Oral Exposure

In humans, barium is predominantly found in bone; approximately 90% of the barium in the body was detected in the bone (Schroeder et al. 1972). Approximately 1–2% of the total body burden was found in muscle, adipose, skin, and connective tissue. This information is supported by a number of studies

(Bauer et al. 1957; Losee et al. 1974; Miller et al. 1985; Sowden 1958; Sowden and Stitch 1957; Sowden and Pirie 1958). Significant increases in the levels of barium in bone were found in rats administered barium chloride in the diet or barium as a component of Brazil nuts for 29 days (Stoewsand et al. 1988); this study did not examine other tissues. A study by McCauley and Washington (1983) in which rats were exposed to barium chloride and barium carbonate in drinking water found the following non-skeletal distribution (skeletal tissue was not examined in the study) 24 hours after ingestion: heart > eye > skeletal muscle > kidney > blood > liver.

3.4.2.3 Dermal Exposure

No studies were located regarding distribution of barium in humans or animals after dermal exposure.

3.4.2.4 Other Routes of Exposure

Human injection studies support the findings of the inhalation and oral exposure studies. Barium is rapidly cleared from the blood and distributed to bone (Bauer et al. 1957; Harrison et al. 1966, 1967; Newton et al. 1991). A long-term study of barium retention in humans injected with ^{133}Ba found that after the first couple of years, bone turnover was the most significant contributor to barium losses from the skeleton (Newton et al. 2001).

3.4.3 Metabolism

Barium is not metabolized in the body, but it may be transported or incorporated into complexes or tissues.

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

No studies have been located regarding excretion of barium following inhalation exposure in humans. Studies in animals demonstrate that the fecal excretion of barium exceeds urinary excretion (Cember et al. 1961; Cuddihy and Griffith 1972; Cuddihy et al. 1974). In dogs, 30% of the total barium excretion was accounted for by urine (Morrow et al. 1964).

3.4.4.2 Oral Exposure

A study of two humans ingesting a normal diet found that fecal excretion of barium was 2–3 times higher than urinary excretion over a 30-day period (Tipton et al. 1966). A 29-day rat study also demonstrated that the feces was the primary route of excretion following exposure to barium chloride in the diet or barium from brazil nuts (Stoewsand et al. 1988).

3.4.4.3 Dermal Exposure

No studies were located regarding excretion of barium in humans or animals after dermal exposure.

3.4.4.4 Other Routes of Exposure

Several human studies have examined the excretion of barium following parenteral administration. These studies confirm the findings of the inhalation or oral exposure studies that barium is primarily excreted in the feces. In a study, one subject receiving an intravenous injection of ^{133}Ba, 84% of the radiolabelled barium was excreted within the first 6 days, primarily in the feces (75% of total dose) (Harrison et al. 1967; Newton et al. 1977). The ratio of fecal to urinary barium excretion in six subjects injected with ^{133}Ba ranged from 6 to 15 for the first 2 weeks (Newton et al. 1991).

A study in rats (Edel et al. 1991) found that biliary excretion did not significantly contribute to the total amount of barium excreted in the feces, suggesting that other physiological routes were responsible for fecal barium. A study of rabbits administered an intravenous injection of radiolabelled barium also found that barium was primarily excreted in the feces. After the first day, fecal excretion was approximately twice as high as urinary excretion. The barium was primarily excreted in the first 5 days after exposure; after 9 days, approximately 50% of the dose was excreted (Liniecki 1971).

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

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

pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 1994; Andersen et al. 1987). 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 parameterization, (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 3-2 shows a conceptualized representation of a PBPK model.

If PBPK models for barium 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.

No information on available PBPK models for barium has been identified.

3.5 MECHANISMS OF ACTION

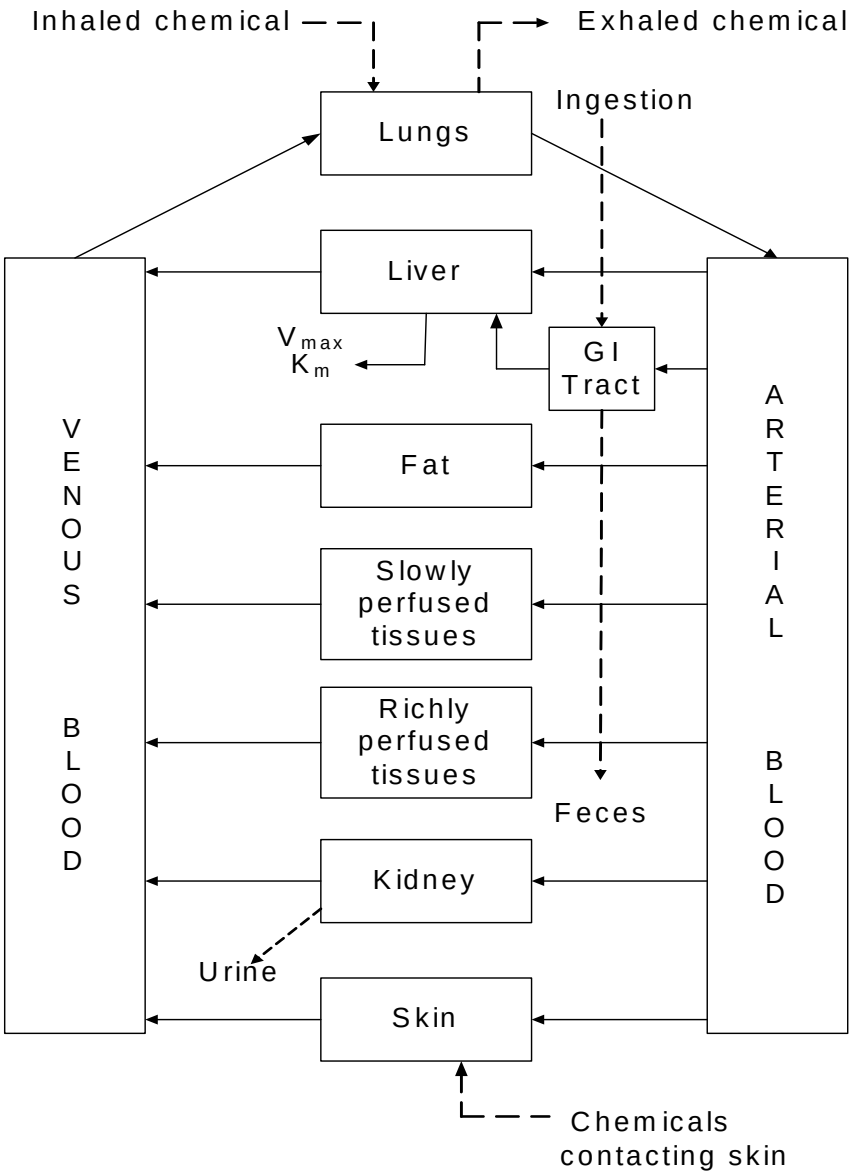
3.5.1 Pharmacokinetic Mechanisms

No studies were located for animals or humans that describe observed mechanisms for barium absorption across the skin, lung, or gut or barium distribution, metabolism, or excretion.

3.5.2 Mechanisms of Toxicity

The mechanism of barium toxicity has not been fully elucidated. Presumably, high-dose exposure to barium consistently results in a number of effects including ventricular tachycardia, hypertension and/or hypotension, and muscle weakness and paralysis (Deng et al. 1991; Diengott et al. 1964; Downs et al. 1995; Gould et al. 1973; Jha et al. 1993; Koch et al. 2003; Talwar and Sharma 1979; Wetherill et al. 1981). There is strong evidence that many of these effects result from increases in intracellular potassium levels. Barium is a competitive potassium channel antagonist that blocks the passive efflux of intracellular potassium, resulting in a shift of potassium from extracellular to intracellular compartments (Roza and Berman 1971). The intracellular translocation of potassium results in a decreased resting membrane potential, making the muscle fibers electrically unexcitable and causing paralysis (Koch et al. 2003). Hypokalemia (serum potassium levels below 3.5 mEq/L) has been reported in a number of individuals exposed to high doses of barium (Deng et al. 1991; Diengott et al. 1964; Downs et al. 1995; Gould et al. 1973; Jha et al. 1993; Koch et al. 2003; Lewi and Bar-Khayim 1964; Phelan et al. 1984; Talwar and Sharma 1979; Wetherill et al. 1981). Intravenous infusion of potassium often relieves many of the symptoms of barium toxicity (Dreisbach and Robertson 1987; Haddad and Winchester 1990; Proctor et al. 1988). However, there is also evidence that some of these effects may be due to barium-induced neuromuscular blockade and membrane depolarization (Phelan et al. 1984; Thomas et al. 1998). Two investigators (Phelan et al. 1984; Thomas et al. 1998) have shown an apparent direct relationship

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



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.

Source: adapted from Krishnan and Andersen 1994

between serum barium levels and the degree of paralysis or muscle weakness in two individuals orally exposed to barium.

3.5.3 Animal-to-Human Extrapolations

Most of the available data in humans comes from case reports involving acute oral exposure to presumably high doses of barium; the primary effects noted were gastrointestinal distress and effects associated with hypokalemia (e.g., ventricular tachycardia, hypo or hypertension, paralysis). Only one human exposure study (Wones et al. 1990) provided reliable information on exposure level; this study did not find any significant alterations in blood pressure in subjects exposed to relatively low doses of barium. The available data in laboratory animals suggest that toxicity of ingested barium is similar across species. Studies conducted by the NTP (1994) in rats and mice found similar targets of toxicity; although some differences in sensitivity were found between the species. Following intermediate-duration exposure, renal effects were observed at lower doses in rats (115 mg barium/kg/day) than in mice (450 mg barium/kg/day). However, NTP (1994) concluded that rats and mice were equally sensitive to the barium-induced renal effects because adverse effect levels when estimated on a per unit surface area basis were similar for the two species. In the absence of contrary data, it is assumed that humans and animals would have similar targets of toxicity and equal sensitivity.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

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

chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No studies were located regarding endocrine disruption in human and/or animals after exposure to barium; additionally, *in vitro* studies were not located.

3.7 CHILDREN'S SUSCEPTIBILITY

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

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

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life, and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage

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

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

There is limited information on age-related differences in the toxicity of barium in humans or animals. Deng et al. (1991) and Lewi and Bar-Khayim (1964) reported cases from two food poisoning incidents that involved exposure of adults and children. Both reports noted that children did not seem to be affected by the barium carbonate exposure; however, these data should be interpreted cautiously because neither involved examination of exposed children and no information is available on barium carbonate intake. There are limited data on the developmental toxicity of barium in laboratory animals. The body weights of the offspring of rats exposed to barium chloride prior to mating were significantly lower than

control pup body weights. A decrease in litter size was also observed, although the difference was not statistically significant (Dietz et al. 1992). No developmental effects were observed in the offspring of mice exposed to barium chloride prior to mating (Dietz et al. 1992). Reduced survival and decreased body weight were observed in the offspring of rats exposed to barium carbonate dust (Tarasenko et al. 1977); however, poor reporting of the study methods and results limits the interpretation of the Tarasenko et al. (1977) study.

There are some data suggesting possible age-related differences in toxicokinetic properties of barium. A higher rate (about 10 times higher) of absorption was found in younger rats compared to older rats (Taylor et al. 1962). A study of cadmium and mercury also found higher permeability in the jejunum of immature rats as compared to mature animals (Foulkes and Bergman 1993). An unpublished study by Della Rosa summarized by ICRP (1993) found higher barium retention in dogs aged 43 (2.3% retained) or 150 (2.0%) days, compared to dogs aged 250 days (0.8%) or adult dogs (0.4–0.6%). Information on biomarkers, interactions, and methods for reducing toxic effects of barium (discussed in Sections 3.8, 3.10, and 3.11) comes from studies in adults and mature animals; no child-specific information was identified. In the absence of data to the contrary, it is assumed that this information will also be applicable to children.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

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

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, 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 barium are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by barium are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10, Populations That Are Unusually Susceptible.

At present, there are no well-established biomarkers of exposure and effect for barium. Data suggesting possible biomarkers are presented below.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Barium

Barium can be measured in bone, blood, urine, and feces. It has been shown to be sequestered in bone and teeth and excreted in feces and urine. Background levels of barium in bone are approximately 2 µg/g wet weight (ICRP 1974; Schroeder et al. 1972). Background levels of barium in blood, urine, and feces will vary with daily intake of barium. However, the following levels have been reported: bone, 2 ppm (ICRP 1974; Schroeder et al. 1972); feces, 690–1,215 µg/day (ICRP 1974; Schroeder et al. 1972; Tipton et al. 1969); and urine, 17–50 µg/day (ICRP 1974; Schroeder et al. 1972; Tipton et al. 1969). In the United States, the geometric mean concentration of barium in the urine is approximately 1.5 µg/L (CDC 2005). There are no data correlating bone, blood, urine, or feces levels of barium with specific exposure levels. For more detailed information on the toxicokinetics of barium, see Section 3.4.

3.8.2 Biomarkers Used to Characterize Effects Caused by Barium

Reports of individuals exposed to high levels of barium suggest that cardiovascular, nervous, and gastrointestinal systems are targets of barium toxicity (Das and Singh 1970; Deng et al. 1991; Diengott et al. 1964; Downs et al. 1995; Gould et al. 1973; Jha et al. 1993; Koch et al. 2003; Lewi and Bar-Khayim 1964; McNally 1925; Ogen et al. 1967; Phelan et al. 1984; Talwar and Sharma 1979; Wetherill et al. 1981). The likely cause of most of these effects is barium induced hypokalemia. Gastrointestinal disturbances are usually the first symptoms of acute barium exposure. Hypokalemia, hypertension, and abnormalities in heart rhythm frequently occur shortly afterwards. General muscle weakness is a frequent symptom, sometimes followed by paralysis. Nerve conduction is often affected, resulting in numbness and tingling of the mouth, neck and extremities. Loss of deep tendon reflexes may also occur. Not all symptoms appear in every case of acute barium poisoning. Although the observation of hypokalemia and gastrointestinal upset may be indicative of exposure to high doses of barium, other toxicants and disease states can produce these effects.

Animal studies also suggest that the kidney is a target of barium toxicity; the observed nephropathy is not specific to barium and would not be a sensitive biomarker of effect.

3.9 INTERACTIONS WITH OTHER CHEMICALS

There are no data regarding the interaction between barium and various chemicals potentially found at hazardous waste sites. However, there are data that suggest that barium may interact with other cations and certain prescription drugs. Drug interactions are of relevance because individuals exposed to barium by living or working near hazardous waste sites contaminated with this substance may also be taking prescription drugs.

The cations potassium, calcium, and magnesium also interact with barium. Barium exposure, for example, may cause a buildup of potassium inside the cell resulting in extracellular hypokalemia, which is believed to mediate barium-induced paralysis. In fact, potassium is a powerful antagonist of the cardiotoxic and paralyzing effects of barium in animals (Foster et al. 1977; Jaklinski et al. 1967; Roza and Berman 1971; Schott and McArdle 1974) and is used as an antidote in cases of acute barium poisoning. Calcium and magnesium suppress uptake of barium by pancreatic islets *in vitro*. Conversely, barium, in low concentrations, stimulates calcium uptake in these cells. Although the data are insufficient to

determine the significance of these findings to human health effects, displacement of calcium may be the mechanism by which barium stimulates insulin release (Berggren et al. 1983).

Among the drugs that are known to interact with barium, the barbiturates sodium pentobarbital and phenobarbital, were found to have an increased depressive effect on the hearts of rats exposed to barium (Kopp et al. 1985; Perry et al. 1983, 1989). This hypersensitivity of the cardiovascular system to anesthesia was not observed in similarly treated animals that were anesthetized with xylazine plus ketamine. Results of the study indicated that the hypersensitivity was specific to the barbiturates and not a generalized effect of anesthesia (Kopp et al. 1985).

Other medically prescribed drugs interact with barium. Experiments with mice indicated that atropine significantly antagonized antinociception and death induced by intracerebroventricular injection of barium chloride (Segreti et al. 1979; Welch et al. 1983). These same studies also found that naloxone, a narcotic antagonist, inhibited the lethal toxicity of barium (Segreti et al. 1979; Welch et al. 1983). Propranolol had no effect on barium-induced paralysis in rats (Schott and McArdle 1974). Verapamil rapidly abolished cardiac dysrhythmias in rabbits injected with barium chloride (Mattila et al. 1986). In the same study, pretreatment with the tricyclic antidepressant, doxepin, was found to offer some protection against barium-induced dysrhythmias (Mattila et al. 1986). Ouabain, which is an inhibitor of Na^+-K^+ ATPase, while not widely prescribed, has been shown to rapidly reverse the paralyzing effects of barium. It has been hypothesized that ouabain works by reducing barium-induced hypokalemia by allowing some intracellular potassium to escape. However, this hypothesis has not yet been proved or disproved because of the complexity of the mechanism involved (Schott and McArdle 1974).

Other substances can affect barium pharmacokinetics. One study showed that sodium alginate could reduce retention of orally administered barium, possibly by inhibiting absorption in the gut (Sutton et al. 1972). This could be useful in treating cases of acute barium ingestion. Lysine and lactose increase absorption of barium and could increase the toxic effects of oral exposure (Lengemann 1959).

A human study involving one adult female was performed by applying barium chloride, alone and in combination, with dimethyl sulfoxide to the cervical epithelium. Dimethyl sulfoxide significantly enhanced the ability of barium chloride to induce dysplasia with unusual cell formation in the cervical epithelium (Ayre 1966). The significance of this is difficult to determine since there was only one subject, there were no controls, and few details of the experiment were provided.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to barium than will most persons exposed to the same level of barium in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of barium, or compromised function of organs affected by barium. Populations who are at greater risk due to their unusually high exposure to barium are discussed in Section 6.7, Populations with Potentially High Exposures.

The limited data available suggest that certain subgroups of the population may be more susceptible to barium exposure than the general population. These include people with cardiovascular problems or lung disease, those taking certain prescription drugs, children, pregnant women, and smokers.

Animal studies suggest that the kidney may be a sensitive target of barium toxicity; thus, individuals with impaired renal function may have a higher risk of developing barium-induced kidney damage. There is suggestive evidence that barium may affect blood pressure. Therefore, humans with hypertension could be at increased risk from either chronic, intermediate, or acute barium exposure. Barbiturates have been shown to have an enhanced depressant effect on the heart in barium-exposed animals (Kopp et al. 1985; Perry et al. 1983, 1989). Individuals on this type of medication may experience an increased risk of heart problems on exposure to barium.

Since exposure to high doses of barium has been repeatedly demonstrated to significantly decrease serum potassium in both humans and animals (Foster et al. 1977; Gould et al. 1973; Phelan et al. 1984; Roza and Berman 1971), individuals taking diuretics may have a more severe hypokalemic reaction to barium toxicity.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to barium. 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 barium. 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 barium:

Dreisbach RH, Robertson WO, eds. 1987. Handbook of poisoning: Prevention, diagnosis and treatment. 12th ed. Norwalk, CT: Appleton & Lange, 119-120.

Haddad LM, Winchester JF, eds. 1990. Clinical management of poisoning and drug overdose. 2nd ed. Philadelphia, PA: WB Saunders Company, 1129.

3.11.1 Reducing Peak Absorption Following Exposure

The general population is typically exposed to barium through consumption of food and drinking water; workers may also be exposed to barium via inhalation or dermal contact. General recommendations for reducing absorption of barium following exposure have included removing the exposed individual from the contaminated area and removing contaminated clothing, followed by washing with mild soap and water. If the eyes and skin were exposed, they are flushed with water. Lavage or emesis has also been suggested; however, high concentrations of barium cause nausea and emesis should not be induced in cases where substantial vomiting has already occurred (Haddad and Winchester 1990). Furthermore, there is a risk of aspiration of vomitus during emesis. Administration of soluble sulfates orally will also limit absorption of barium by causing precipitation of an insoluble form of barium (barium sulfate) (Dreisbach and Robertson 1987; Haddad and Winchester 1990). However, intravenous administration of sulfate salts should be avoided because barium precipitate in the kidneys will cause renal failure (Dreisbach and Robertson 1987; Koch et al. 2003).

3.11.2 Reducing Body Burden

Barium is primarily distributed to the bone and teeth; it is not known if the barium distributed to these tissues would result in toxicity. A method for reducing the levels of barium in bone and teeth has not been identified. Removal of barium from the bloodstream may be facilitated by infusing with saline and inducing saline diuresis (Dreisbach and Robertson 1987). As described in several case reports of barium poisoning (Bahlmann et al. 2005; Koch et al. 2003; Thomas et al. 1998; Wells and Wood 2001), hemodialysis resulted in significant decreases in the levels of barium in the blood and improved clinical signs.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

Hypokalemia is commonly seen in cases of acute barium toxicity and may be responsible for some of the symptoms of barium poisoning (Proctor et al. 1988). Plasma potassium should be monitored and hypokalemia may be relieved by intravenous infusion of potassium (Dreisbach and Robertson 1987; Haddad and Winchester 1990; Proctor et al. 1988).

3.12 ADEQUACY OF THE DATABASE

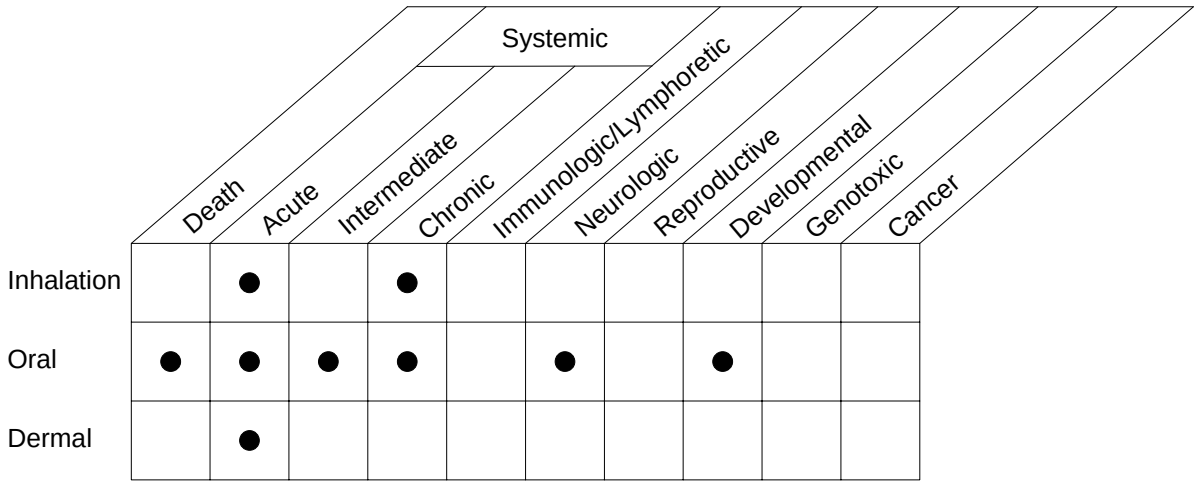
Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of barium and compounds is available. Where adequate information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

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

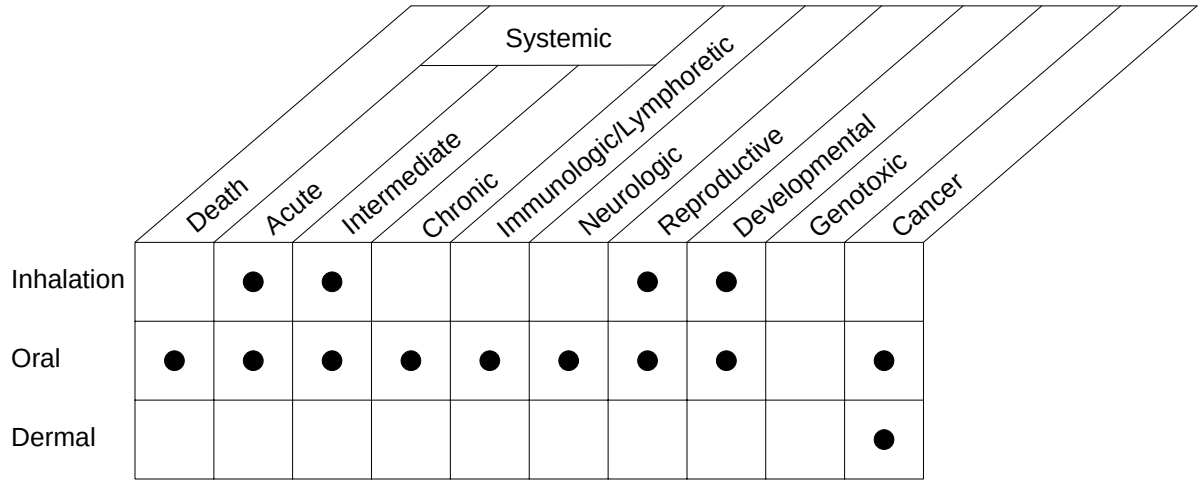
3.12.1 Existing Information on Health Effects of Barium and Barium Compounds

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

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



Human



Animal

● Existing Studies

There is little information regarding health effects in humans following inhalation, oral, or dermal exposure to barium and barium compounds (Figure 3-3). Inhalation studies are limited to several case reports of individuals exposed acutely or chronically through occupational exposure (Doig 1976; Essing et al. 1976; Seaton et al. 1986; Shankle and Keane 1988). A number of case reports of acute oral exposure to high doses of barium have been identified (Das and Singh 1970; Deng et al. 1991; Diengott et al. 1964; Downs et al. 1995; Gould et al. 1973; Jha et al. 1993; Koch et al. 2003; Lewi and Bar-Khayim 1964; McNally 1925; Ogen et al. 1967; Phelan et al. 1984; Talwar and Sharma 1979; Wetherill et al. 1981). Additionally, there is information from a single intermediate-duration experimental study (Wones et al. 1990) and several human epidemiological studies or statistical studies examining mortality and morbidity rates in communities having exposure to barium through drinking water supplies (Brenniman and Levy 1985; Brenniman et al. 1979a, 1979b, 1981; Elwood et al. 1974; Schroeder and Kraemer 1974). Dermal studies are limited to one case report of an exposed individual (Stewart and Hummel 1984).

The majority of studies conducted on animals have been oral exposure studies (Figure 3-3). Available inhalation studies with experimental animals (Hicks et al. 1986; Tarasenko et al. 1977) can only suggest information on the health effects of barium because these studies have a number of limitations and deficiencies; a third inhalation study (Cullen et al. 2000) is limited to the examination of the respiratory tract. The available oral studies have examined a number of end points, although most studies focused on various systemic effects for acute (Borzelleca et al. 1988; Boyd and Abel 1966; Tardiff et al. 1980), intermediate (Dietz et al. 1992; McCauley et al. 1985; NTP 1994; Perry et al. 1983, 1985, 1989; Tarasenko et al. 1977; Tardiff et al. 1980), and chronic exposure (Kopp et al. 1985; McCauley et al. 1985; NTP 1994; Perry et al. 1983, 1985, 1989; Schroeder and Mitchener 1975a, 1975b). Dermal studies with experimental animals are limited to one skin irritation study (Tarasenko et al. 1977) and one study evaluating the tumor-promoting activity of barium (Van Duuren et al. 1968).

3.12.2 Identification of Data Needs

Acute-Duration Exposure. There are limited data on the acute toxicity of barium following inhalation, oral, or dermal exposure. Data on the toxicity of inhaled barium are limited to a human experimental study in which welders were exposed to fumes from barium-containing electrodes (Zschiesche et al. 1992), a case of a worker exposed to a large amount barium carbonate dust (Shankle and Keane 1988), and a study in which guinea pigs were exposed to a single concentration of barium chloride for unspecific amount of time (Hicks et al. 1986). Although none of these studies are suitable for derivation of an MRL, the Hicks et al. (1986) study does identify two potential end points (increased

blood pressure and bronchoconstriction). Additional inhalation studies are needed to fully evaluate the toxicity of barium and establish concentration-response relationships.

Most of the available information on the acute toxicity of barium comes from human case reports involving oral exposure to soluble barium compounds and oral toxicity studies in animals. There are a number of case reports of individuals accidentally or intentionally ingesting large doses of barium (Das and Singh 1970; Deng et al. 1991; Diengott et al. 1964; Downs et al. 1995; Gould et al. 1973; Jha et al. 1993; Koch et al. 2003; Lewi and Bar-Khayim 1964; McNally 1925; Ogen et al. 1967; Phelan et al. 1984; Talwar and Sharma 1979; Wetherill et al. 1981). In general, dose levels were not reported; based on the severity of the observed effects, it is likely that the doses were very high. The observed effects included effects associated with hypokalemia (cardiac arrest, ventricular tachycardia, muscle weakness, and paralysis), gastrointestinal distress (vomiting, gastric pain, and diarrhea), and kidney damage (hemoglobin in the urine, renal insufficiency, degeneration, and acute renal failure). Several studies in experimental animals have examined the acute oral toxicity of barium chloride (Borzelleca et al. 1988; Tardiff et al. 1980). These studies have determined LD_{50} values and evaluated potential systemic, neurological, and reproductive end points. These studies have not consistently identified targets of toxicity or adverse effect levels. The available data were considered inadequate for derivation of an acute oral MRL. Human data consistently identify the gastrointestinal tract as a target of barium toxicity; most case reports of individuals ingesting soluble barium compounds report vomiting, diarrhea, and/or abdominal pain as one of the early signs of toxicity. However, none of the animal studies have adequately investigated this end point; rodents are not a good model for examining gastrointestinal irritation. Animal studies are needed to identify the critical targets of barium toxicity and establish dose-response relationships; these studies should include a more appropriate animal model for investigating potential gastrointestinal effects.

Two studies have examined the dermal toxicity of barium. One is a case report on an individual burned with molten barium chloride (Stewart and Hummel 1984); extrapolation of the results of this study to environmental exposure scenarios is complicated by the thermal burns. Tarasenko et al. (1977) examined the dermal and ocular toxicity of barium carbonate in several animal species. Poor reporting of the experimental design and results limits the interpretation of the study. Additional dermal toxicity studies are needed for several barium compounds to confirm the Tarasenko et al. (1977) study findings that barium is a local irritant and to establish the existence of remote toxicity.

Intermediate-Duration Exposure. No human studies have examined the toxicity of barium in humans following intermediate-duration inhalation exposure. Two animal studies have been identified

(Cullen et al. 2000; Tarasenko et al. 1977). The Tarasenko et al. (1977) study examined systemic, reproductive, and developmental end points. However, interpretation of the results is limited by poor reporting of the study design and results. The Cullen et al. (2000) study only examined the respiratory tract. As these studies were considered inadequate for development of an inhalation MRL, additional studies examining a variety of end points are needed to identify the critical targets of barium toxicity and to establish concentration-response relationships.

One human experimental study examined the cardiovascular toxicity of barium (Wones et al. 1990) following oral exposure; no adverse effects were found. Several animal studies also examined the oral systemic toxicity (McCauley et al. 1985; NTP 1994; Perry et al. 1983, 1985, 1989; Tardiff et al. 1980), neurotoxicity (NTP 1994), reproductive toxicity (Dietz et al. 1992), and developmental toxicity (Dietz et al. 1992; Tarasenko et al. 1977) of barium. The results of these studies suggest that the kidney is the most sensitive target of toxicity following intermediate-duration oral exposure. An intermediate-duration oral MRL based on kidney effects in rats exposed to barium chloride for 13 weeks (NTP 1994) has been derived.

Information on the oral toxicity of barium following intermediate-duration exposure comes from a human experimental study examining cardiovascular toxicity (Wones et al. 1990) and several animal studies examining systemic toxicity (McCauley et al. 1985; NTP 1994; Perry et al. 1983, 1985, 1989; Tardiff et al. 1980), neurotoxicity (NTP 1994), reproductive toxicity (Dietz et al. 1992; NTP 1994), and developmental toxicity (Dietz et al. 1992). The human study did not find significant alterations in blood pressure or ECG readings in adults exposed to fairly low doses (Wones et al. 1990). Effects observed in the animal studies include increased blood pressure (Perry et al. 1983, 1985, 1989), kidney damage (glomerular alterations consisting of fused podocytes and thickening of the capillary basement membrane and mild to moderate nephropathy) (McCauley et al. 1985; NTP 1994), and developmental toxicity (decreased pup birth weight) (Dietz et al. 1992). The increase in blood pressure was observed at the lowest adverse effect level; however, two other studies (McCauley et al. 1985; NTP 1994) did not find significant alterations in blood pressure or ECG readings in rats exposed to higher doses of barium. The low-mineral diet used in the Perry et al. (1983, 1985, 1989) studies may have influenced the results. The calcium content of the rye-based diet was 3.8 mg/kg, which is lower than the concentration recommended for maintenance, growth, and reproduction of laboratory rats (NRC 1995). Additional studies are needed to support this hypothesis. The results of the McCauley et al. (1985) and NTP (1994) studies suggest that the kidney is the most sensitive target of toxicity in rats and mice following intermediate-duration oral

exposure; an intermediate-duration oral MRL was derived based on kidney effects observed in rats exposed to barium chloride for 13 weeks (NTP 1994).

No studies have examined the toxicity in humans or animals following intermediate-duration dermal exposure. Studies are needed to assess the potential toxicity of various barium compounds and to establish whether dermal exposure would result in remote toxicity.

Chronic-Duration Exposure and Cancer. The toxicity of barium following chronic-duration inhalation exposure is limited to three occupational exposure studies (Doig 1976; Essing et al. 1976; Seaton et al. 1986). These studies focused on potential respiratory tract effects and are limited by co-exposure to other compounds, small number of tested workers, and/or lack of a comparison group. Well-designed studies examining a number of potential end points are needed to identify the critical targets of barium toxicity and establish concentration-response relationships. These studies would be useful for deriving a chronic-duration inhalation MRL for barium.

Three groups of investigators have examined the effect of living in a community with elevated barium levels in the drinking water and the risk of mortality and cardiovascular effects (Brenniman and Levy 1985; Brenniman et al. 1979a, 1979b, 1981; Elwood et al. 1974; Schroeder and Kraemer 1974). These studies are limited by a number of factors including the lack of information on barium ingestion levels and the possible use of water softeners, which may have removed barium from the drinking water and increased the sodium content of the water. Several studies in rats and mice have examined the chronic toxicity of barium (NTP 1994; Perry et al. 1989; Schroeder and Mitchener 1975a, 1975b). The Perry et al. (1989) study found significant increases in systolic blood pressure in rats fed a relatively low concentration of barium in the diet; however, the contribution of the low mineral basal diet to the observed effect is not known. Several rat studies did not find adverse effects at the highest doses tested (McCauley et al. 1985; NTP 1994; Schroeder and Mitchener 1975a). Marked renal nephropathy was observed in mice (NTP 1994); this study and effect were the basis of the chronic-duration MRL for barium. The available toxicokinetic data suggest that barium accumulates in bone; it is not known if this accumulation would result in adverse effects. Studies designed to test the possible association between high levels of barium in bone and adverse bone effects would be useful.

Data on the dermal toxicity of barium are limited to a skin tumor promotion study using barium hydroxide extract from tobacco plants (Van Duuren et al. 1968); the study did not examine noncancerous

end points. Additional dermal exposure studies are needed to evaluate whether various barium compounds are irritants and can cause remote-site toxicity.

No studies assessing the carcinogenicity of barium following chronic inhalation exposure were identified. The carcinogenicity of ingested barium has been assessed in several long-term oral exposure studies in rats and mice (McCauley et al. 1985; NTP 1994; Schroeder and Mitchener 1975a, 1975b). These studies did not find significant increases in the incidence of neoplastic lesions in either species. Although a study by Van Duuren et al. (1968) provided evidence suggesting that barium hydroxide extract derived from tobacco leaf may act as a tumor-promoting agent when applied with a tumor initiating agent, there are no studies to assess barium's potential to be a complete carcinogen following dermal exposure. Based on the results of the oral study, it can be predicted that inhalation or dermal exposure to barium would not result in remote site carcinogenicity; however, it is not known if long-term exposure would result in respiratory tract cancer following inhalation exposure or skin cancer following dermal exposure. Inhalation and dermal exposure cancer studies are needed to address these questions.

Genotoxicity. The genotoxicity of barium has not been well characterized. One study used an *in vivo* assay to assess genotoxic potential (Yesilada 2001); increases in somatic mutations were observed in *D. melanogaster* following exposure to high levels of barium nitrate. The available data utilizing *in vitro* assays have not found significant alterations in gene mutation frequency or DNA damage in non-mammalian systems (Kanematsu et al. 1980; Monaco et al. 1990, 1991; Nishioka 1975; NTP 1994; Rossman et al. 1991; Sirover and Loeb 1976a, 1976b). In mammalian test systems, barium did not have clastogenic effects (NTP 1994), but did increase the frequency of gene mutation (NTP 1994). The available data are inadequate to thoroughly assess the genotoxic potential of barium; additionally studies, particularly *in vivo* assays, are needed.

Reproductive Toxicity. The reproductive effects of barium have not been thoroughly studied. There are no studies regarding reproductive effects in humans following barium exposure. Several animal studies have examined potential end points of reproductive toxicity. In the only inhalation exposure study (Tarasenko et al. 1977), a number of adverse effects were reported, including disturbances in spermatogenesis, shortened estrus cycle, and histological damage to the testes and ovaries. However, limited reporting of the study design and results and the lack of incidence data and statistical analysis limit the interpretation of the study results. Although a 10-day gavage study found significant decreases in relative and absolute ovary weights (Borzelleca et al. 1988), other oral exposure studies have not found alterations in organ weights or histological alterations in reproductive tissues following acute-,

intermediate-, or chronic-duration exposure (McCauley et al. 1985; NTP 1994). Additionally, no alterations in sperm morphology, motility, or counts were observed in rats or mice exposed to barium in drinking water for 60 days (Dietz et al. 1992). Only one oral study evaluated reproductive function (Dietz et al. 1992) and found no alterations in pregnancy rate or gestation length in rats or mice. A two-generation study would be useful for further evaluating the potential reproductive toxicity of barium. No dermal exposure studies examining reproductive end points were identified; based on available toxicokinetic data. Additional studies are needed to further assess if reproductive toxicity is an end point of concern for barium.

Developmental Toxicity. The developmental effects of barium have not been studied extensively in either humans or animals. One limited statistical study evaluated the degree of correlation between barium concentrations in drinking water and human congenital malformation rates of the central nervous system (Morton et al. 1976). Results of the study indicated there was a negative statistical correlation between these parameters, implying that a lower risk of congenital abnormalities was found in populations with higher barium levels. Two animal studies evaluated the potential developmental toxicity of barium. Reduced survival, underdevelopment, lowered body weight, decreased lability of the peripheral nervous system, and various blood disorders were reportedly noted in the offspring of rats following inhalation to barium for an intermediate exposure period (Tarasenko et al. 1977). The investigators also noted increased mortality and systemic toxicity in the offspring of rats orally exposed to barium during conception and pregnancy. As noted previously, interpretation of the results from the Tarasenko et al. (1977) studies are limited because the studies were poorly reported and no incidence data or statistical analysis were reported. In a mating study involving oral exposure to barium chloride prior to mating (Dietz et al. 1992), decreases in pup birth weight and a nonstatistically significant decrease in live litter size were observed in rats; no adverse effects were observed in mice. It is not known if the decrease in body weight observed in the rat offspring was secondary to maternal toxicity or was a direct effect on the fetus. Additional developmental toxicity studies, particularly studies involving oral exposure during gestation and lactation, would be useful to confirm the results of the Tarasenko et al. (1977) and Dietz et al. (1992) studies. Developmental toxicity studies via dermal exposure are also needed because this end point has not been evaluated for this route of exposure.

Immunotoxicity. The effect of barium on the immune system has not been well studied. No studies were available regarding immunological effects in humans or animals following inhalation, oral, or dermal exposure to barium. Several oral exposure studies in animals examining lymphoreticular end points such as thymus and lymph node histopathology have not reported adverse effects at nonlethal

doses (Borzelleca et al. 1988; McCauley et al. 1985; NTP 1994). Screening studies are needed to evaluate the potential immunotoxicity of barium following inhalation, oral, or dermal exposure.

Neurotoxicity. Exposure to high oral doses of barium is associated with numbness and tingling around the mouth and neck (Lewi and Bar-Khayim 1964; Morton 1945); higher doses can result in partial or complete paralysis (Das and Singh 1970; Diengott et al. 1964; Gould et al. 1973; Lewi and Bar-Khayim 1964; Morton 1945; Ogen et al. 1967; Phelan et al. 1984; Wetherill et al. 1981). Absence of a deep tendon reflex has been reported in an individual exposed to airborne barium carbonate powder (Shankle and Keane 1988). Oral exposure of rats and mice to barium has not been associated with changes in brain weight or gross or microscopic lesions of the brain (Borzelleca et al. 1988; McCauley et al. 1985; NTP 1994; Tardiff et al. 1980). NTP (1994) evaluated neurobehavioral performance in rats and mice exposed to barium chloride in drinking water for acute or intermediate durations. Decreases in spontaneous motor activity were observed in rats exposed for an intermediate duration. Decreased grip strength was also observed in mice; however, this was likely due to debilitation rather than neurotoxicity. The human data demonstrate that at presumably high doses, barium affects action potentials of muscles and nerve cells by increasing cellular potassium levels. However, oral studies are needed to establish a dose-response relationship for these neurological effects. No data were available regarding neurological effects in animals following inhalation exposure or humans and/or animals following dermal exposure. Additional studies would be useful to further evaluate the neurotoxic potential of barium.

Epidemiological and Human Dosimetry Studies. A limited number of epidemiological and human dosimetry studies evaluating the health effects of barium are available (Brenniman and Levy 1985; Brenniman et al. 1979a, 1979b, 1981; Elwood et al. 1974; Schroeder and Kraemer 1974; Wones et al. 1990). These studies have primarily focused on the potential of barium to adversely affect cardiovascular function by altering blood pressure or increasing the risk of death due to cardiovascular disease; consistent results have not been found. However, all of the available human studies on barium have limitations and/or confounding variables that make it difficult to draw firm conclusions regarding the health effects of barium (see Sections 3.2.2.1 and 3.2.2.2 for discussions on the specific limitations associated with available epidemiological and human dosimetry studies). Several human studies have also examined the potential toxicity of inhaled barium to the respiratory tract or cardiovascular system (Doig 1976; Essing et al. 1976; Seaton et al. 1986). As with the oral studies, limitations in the study reporting or confounding variables preclude using the studies to establish causal relationships. In addition to these epidemiological or experimental studies, there are numerous case reports of individuals ingesting large doses of barium (Das and Singh 1970; Deng et al. 1991; Diengott et al. 1964; Downs et al. 1995;

Gould et al. 1973; Koch et al. 2003; Lewi and Bar-Khayim 1964; McNally 1925; Ogen et al. 1967; Phelan et al. 1984; Talwar and Sharma 1979; Wetherill et al. 1981) or exposed to airborne barium carbonate (Shankle and Keane 1988). In general, these studies reported serious health effects such as death, ventricular tachycardia, and paralysis. Animal studies provide evidence that the kidney is a sensitive target of toxicity; there is also some evidence that the cardiovascular and neurological systems and the developing organisms are targets of barium toxicity (Dietz et al. 1992; McCauley et al. 1985; NTP 1994; Perry et al. 1983, 1985, 1989). Additional epidemiological and/or human dosimetry studies would be useful to determine the effects of low doses of barium on these end points. Studies of workers exposed to airborne barium would also be useful for establishing the toxicity of barium to the respiratory tract.

Biomarkers of Exposure and Effect.

Exposure. There are no established biomarkers of exposure for barium. Analytical methods exist for measuring barium in blood, urine, feces, and biological tissues (Mauras and Allain 1979; Schramel 1988; Shiraishi et al. 1987); however, there are no data correlating levels of barium in these tissues and fluids with exposure. Studies associating barium levels in biological media (such as blood or urine) with exposure concentrations or doses would be useful for establishing biomarkers of exposure.

Effect. Symptoms of barium toxicity, such as hypokalemia, gastrointestinal upset, hyper- or hypotension, ventricular tachycardia, and numbness and tingling around the mouth and neck (Das and Singh 1970; Deng et al. 1991; Diengott et al. 1964; Downs et al. 1995; Gould et al. 1973; Koch et al. 2003; Lewi and Bar-Khayim 1964; McNally 1925; Ogen et al. 1967; Phelan et al. 1984; Talwar and Sharma 1979; Wetherill et al. 1981) are well documented. However, there are no quantitative studies correlating these effects with dose and these effects are not specific to barium toxicity. For purposes of facilitating medical surveillance, studies to determine useful biomarkers of effect for barium, particularly effects associated with low doses of barium, would be useful.

Absorption, Distribution, Metabolism, and Excretion. The database on absorption, distribution, metabolism, and excretion of barium is limited. Existing studies indicate that barium is absorbed from the respiratory tract (Cuddihy and Griffith 1972; Cuddihy and Ozog 1973b; Morrow et al. 1968) and gastrointestinal tract (Cuddihy and Griffith 1972; Harrison et al. 1956; Leggett 1992; LeRoy et al. 1966; Schroeder et al. 1972; Taylor et al. 1962;Tipton et al. 1969), primarily deposited in the bones and teeth (Bauer et al. 1957; Cuddihy and Griffith 1972; Losee et al. 1974; Miller et al. 1985; Sowden 1958;

Sowden and Pirie 1958; Sowden and Stitch 1957), and excreted mostly in feces and urine (Cuddihy and Griffith 1972; Tipton et al. 1966). Deposition in bones and teeth and excretion in feces and urine appear to be independent of the route of exposure. Essentially no data exist on absorption, distribution, or excretion following dermal exposure; however, this route is not considered to be a significant source of exposure to barium. No significant data exist on the metabolism of barium compounds in the body. Additional studies evaluating the binding and/or complexing of barium and barium compounds with biological macromolecules or organic molecules in the body would be useful. Studies quantifying the extent of absorption following inhalation, oral, and dermal exposure also would be useful because of limited absorption data. A wide variety of individual differences in absorption efficiencies have been detected in the available human studies; studies examining factors influencing barium absorption would be useful.

Comparative Toxicokinetics. Based on available data, there do not appear to be significant differences in the toxicokinetics of barium between species (Chou and Chin 1943; Cuddihy and Griffith 1972; McCauley and Washington 1983), although there is some indication that a larger percentage of absorbed barium is excreted in the feces of humans compared to that of experimental animals. However, there are not enough similar studies on different species to determine this with certainty. Studies on different species would increase confidence in the reliability of the existing database.

Methods for Reducing Toxic Effects. Methods have been reported for limiting oral and dermal absorption of barium compounds (Bronstein and Currance 1988; Dreisbach and Robertson 1987; Haddad and Winchester 1990) and for counteracting the hypokalemia that is produced by barium in acute high-level exposure situations (Dreisbach and Robertson 1987; Haddad and Winchester 1990; Proctor et al. 1988). Contradictions exist in the literature regarding the efficacy or desirability of administering emetics (Bronstein and Currance 1988; Ellenhorn and Barceloux 1988; Haddad and Winchester 1990). Additional studies clarifying this issue would be helpful. Also, studies directed at finding a more efficient way to remove barium from the body would be useful. It is unclear whether mechanisms other than hypokalemia contribute to the toxic effects produced in acute high-level exposure situations. Additional information on the mechanisms responsible for the toxic effects of barium could aid in the development of effective treatments. Magnesium has been reported to antagonize the neuromuscular effects (Dreisbach and Robertson 1987). Additional studies examining the efficacy of administering soluble magnesium salts to antagonize the effects of barium would also be helpful. No information was located on treatment strategies for long-term low-level exposures. Research on procedures for mitigating such chronic exposure situations would be helpful.

Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

There is very little information on the toxicity of barium in children. Two reports of food poisonings with barium carbonate (Deng et al. 1991; Lewi and Bar-Khayim 1964) provide some suggestive information that children may not be as sensitive as adults to barium carbonate toxicity; however, the lack of detailed examination of the exposed children and lack of exposure information limits the interpretation of these data. No human or animal toxicity studies have been designed to assess possible differences in the toxicity of barium. There is some information suggesting that infants and young children may have a higher barium absorption rate than adults (ICRP 1993; Taylor et al. 1962). Other potential toxicokinetic differences have not been thoroughly investigated. Additional studies are needed to evaluate potential age-specific differences in toxicity and toxicokinetics.

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

3.12.3 Ongoing Studies

No ongoing studies were reported in the FEDRIP (2006) database.

4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Barium is an alkaline earth metal with an atomic number of 56 and is classified in Group IIA of the periodic table of elements. Its outer shell of electrons has a $6s^2$ configuration. Because barium is highly reactive, it exists in the environment in the +2 oxidation state, which is its only oxidation state.

Barium forms useful alloys with aluminum and magnesium, which are used as getters in electronic tubes to remove residual gases (Genter 2001). Barium is also used as a deoxidizer for steel and other metals (Boffito 2002).

Barium reacts with several other elements to form commercially-important compounds. Of these, eight barium compounds are covered in this chapter: barium acetate, barium carbonate, barium chloride, barium cyanide, barium, hydroxide, barium oxide, barium sulfate, and barium sulfide. Their chemical formulas, structures, synonyms, and identification numbers, in addition to those for barium metal, are listed in Table 4-1.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Metallic barium is a silvery-white soft metal, but takes on a silver-yellow color when exposed to air (Boffito 2002; Genter 2001). Like other alkaline earth metals, barium decomposes in water, evolving hydrogen gas. Barium oxidizes readily in moist air. In powdered form, barium reacts violently with air. Because of its high reactivity, barium does not exist as the metal in the environment; it exists in a combined state with other elements.

The barium compounds, barium acetate, barium chloride, barium cyanide, barium hydroxide, and barium oxide, are quite soluble in water. Barium carbonate and sulfate are poorly soluble in water. Barium oxide reacts rapidly with carbon dioxide in water to form barium hydroxide and barium carbonate (Dibello et al. 2003). Barium sulfide slowly decomposes in water, forming barium hydroxide and barium hydrosulfide. Barium sulfide is also known to undergo slow oxidation in solution to form elemental sulfur and various oxidized sulfur species including the sulfite, thiosulfate, polythionates, and sulfate. The water solubility of barium compounds increases with decreasing pH (IPCS 1991).

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

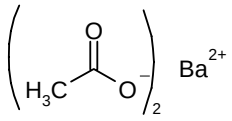
Characteristic	Barium	Barium acetate	Barium carbonate
Synonyms	No data	Acetic acid, barium salt; barium diacetate	Carbonic acid, barium salt; barium monocarbonate; Pigment White 10; BW-C3; BW-P
Trade names	No data	No data	No data
Chemical formula	Ba	$Ba(C_2H_3O_2)_2$	$BaCO_3$
Chemical structure	Ba		$[Ba^{2+}]\ [CO_3^{2-}]$
Identification numbers:			
CAS registry	7440-39-3	543-80-6	513-77-9
NIOSH RTECS	CQ8370000[b]	AF4550000[b]	CQ8600000[b]
EPA hazardous waste	D005	No data	D005
DOT/UN/NA/IMCO shipping	UN1440/IMO 4.3	No data	UN 1564/IMO 6.1
HSDB	4481	No data	950
EINECS	231-149-1	208-849-0	208-167-3
NCI	No data	No data	No data

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

Characteristic	Barium chloride	Barium cyanide	Barium hydroxide
Synonyms	Barium dichloride; NCI-C61074; SBa 0108E	Barium dicyanide	Barium dihydroxide; barium hydroxide lime; caustic baryta
Trade names	No data	No data	No data
Chemical formula	$BaCl_2$	$Ba(CN)_2$	$Ba(OH)_2$
Chemical structure	$[Ba^{2+}]\ [Cl^-]_2$	$[Ba^{2+}]\ [CN^-]_2$	$[Ba^{2+}]\ [OH^-]_2$
Identification numbers:			
CAS registry	10361-37-2	542-62-1	17194-00-2
NIOSH RTECS	CQ8750000[b]	CQ8785000[b]	CQ9200000[b]
EPA hazardous waste	D005	PO13/D003/D005	D005
DOT/UN/NA/IMCO shipping	UN 1564/IMO 6.1	UN 1565/IMO 6.1	UN 1564/IMO 6.1
HSDB	2633	403	1605
EINECS	233-788-1	208-822-3	241-234-5
NCI	No data	No data	No data

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

Characteristic	Barium oxide	Barium sulfate	Barium sulfide
Synonyms	Barium monoxide; barium protoxide; baryta; calcined baryta	Artificial heavy spar; artificial barite; baridol; barytes; blanc fixe; C.I. Pigment White 21; Citobaryum; Enamel White; E-Z-Paque; Solbar; precipitated barium sulphate; sulfuric acid, barium salt[f]	Barium suphide
Trade names	No data	No data	No data
Chemical formula	BaO	$BaSO_4$	BaS
Chemical structure	$[Ba^{2+}]$ $[O^{2-}]$	$[Ba^{2+}]$ $[SO_4^{2-}]$	$[Ba^{2+}]$ $[S^{2-}]$
Identification numbers:			
CAS registry	1304-28-5	7727-43-7	21109-95-5
NIOSH RTECS	CQ9800000[b]	CR0600000[b]	CR0660000[b]
EPA hazardous waste	No data	D005	No data
DOT/UN/NA/IMCO shipping	UN1884	UN1564/IMO6.1	UN1564/IMDG6.1[c]
EINECS	215-127-9	231-784-4	244-214-4
HSDB	No data	5041	No data
NCI	No data	No data	No data

[a]All information obtained from HSDB 2007 and ChemIDplus 2007 except where noted
[b]RTECS 2007
[c]Kresse et al. 2007

CAS = Chemical Abstracts Service; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/Intergovernmental Maritime Dangerous Goods Code; EINECS = European Inventory of Existing Commercial chemical Substances; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; RTECS = Registry of Toxic Effects of Chemical Substances

4. CHEMICAL AND PHYSICAL INFORMATION

Information regarding the physical and chemical properties of barium and barium compounds is located in Table 4-2.

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

Property	Barium	Barium acetate	Barium carbonate
Molecular weight	137.327	255.416 (anhydrous) 273.431 (monohydrate)	197.336
Physical description	Silvery-yellow metal; cubic	White powder (anhydrous); white crystals (monohydrate)	White orthorhombic crystals
Melting point	727 °C	Decomposes at 110 °C (monohydrate)	1,555 °C
Boling point	1,897 °C	No data	No data
Density	3.62 g/cm^3	2.47 g/cm^3 (anhydrous); 2.19 g/cm^3 (monohydrate)	4.2865 g/cm^3
Specific gravity	No data	2.02 (below 24.7 °C)[b]	No data
Odor	No data	No data	Odorless[c]
Odor threshold	No data	No data	No data
Solubility:			
Water	Reacts with water	79.2 g/100 g water at 25 °C	0.0014 g/100 g water at 20 °C; soluble in dilute HCl, HNO_3, and acetic acid[d]; soluble in NH_4Cl and NH_4NO_3 solutions[d]
Organic solvents	Slightly soluble in ethanol	Slightly soluble in ethanol (monohydrate)	Insoluble in alcohol[e]
Partition coefficients	No data	No data	No data
Vapor pressure	6.65x10^{-4} mmHg (at 630 °C)[f]; 0.998 mmHg (at 1,050 °C)[f]	No data	Essentially zero[g]
Henry's law coefficients	No data	No data	No data
Autoignition temperature	No data	No data	Nonflammable[c]
Flashpoint	No data	No data	Nonflammable[c]
Flammability limits	Explosion hazard if exposed to moist air[d]	No data	Nonflammable[c]
Conversion factors	No data	No data	No data
Explosive limits	No data	No data	No data

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

Property	Barium chloride	Barium cyanide	Barium hydroxide
Molecular weight	208.232 (anhydrous); 244.263 (dihydrate)[e]	189.361	171.342 (anhydrous); 189.357 (monohydrate); 315.464 (octahydrate)
Physical description	White hygroscopic orthorhombic crystals (anhydrous); white monoclinic crystals (dihydrate)	White crystalline powder	White powder (anhydrous, monohydrate); white monoclinic crystals (octahydrate)
Melting point	962 °C (anhydrous); decomposes at approximately 120 °C (dihydrate)	No data	408 °C (anhydrous); decomposes at 78 °C (octahydrate)
Boling point	1,560 °C (anhydrous)	No data	No data
Density	3.9 g/cm^3 (anhydrous); 3.097 g/cm^3 (dihydrate)	No data	3.743 g/cm^3 (monohydrate); 2.18 g/cm^3 (octahydrate)
Specific gravity	No data	No data	4.495 (anhydrous)[h]
Odor	Odorless[g]	No data	No data
Odor threshold	No data	No data	No data
Solubility:			
Water	37.0 g/100 g water at 25 °C	800 g/L (at 14 °C)[e]	4.91 g/100 g water at 25 °C
Organic solvents	Insoluble in ethanol (dehydrate)	180 g/L (in 70% alcohol at 14 °C)[e]	Soluble in methanol[d]
Partition coefficients	No data	No data	No data
Vapor pressure	Essentially zero[g]	No data	0 mm Hg at 15 °C (monohydrate)[i]; 11.4 mm Hg at 15 °C (water vapor pressure of octahydrate)[i]
Henry's law coefficients	No data	No data	No data
Autoignition temperature	No data	Nonflammable[c]	No data
Flashpoint	No data	Nonflammable[c]	No data
Flammability limits	No data	Nonflammable[c]	No data
Conversion factors	No data	No data	No data
Explosive limits	No data	No data	Explosive >216 °C[j]

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

Property	Barium oxide	Barium sulfate	Barium sulfide
Molecular weight	153.326	233.391	169.393
Physical description	White-yellow powder; cubic and hexagonal crystals	White orthorhombic crystals	Colorless cubic crystals or gray powder
Melting point	1,972 °C	1,580 °C	2,229 °C
Boling point	No data	No data	No data
Density	5.72 g/cm^3 (cubic)	4.49 g/cm^3	4.3 g/cm^3
Specific gravity	5.32 (hexagonal)[b]	4.50[b]	No data
Odor	Odorless[g]	Odorless[d]	Sulfurous
Odor threshold	No data	No data	No data
Solubility:			
Water	1.5 g/100 g water at 20 °C	00.00031 g/100 g water at 20 °C	8.94 g/100 g water at 25 °C
Organic solvents	Soluble in ethanol; insoluble in acetone	Insoluble in ethanol	No data
Partition coefficients	No data	No data	No data
Vapor pressure	Essentially zero[g]	No data	No data
Henry's law coefficients	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	Produces heat on contact with water or steam[k]	Noncombustible[k]	Flammable by spontaneous chemical reactions[k]
Conversion factors	No data	No data	No data
Explosive limits	Contact with CO_2 may cause explosion[k]	Heating with aluminum may cause violent explosions[k]	Air, moisture, or acid fumes may cause it to ignite[k]

[a]All information obtained from Lide 2005 except where noted
[b]Dibello et al. 2003
[c]DOT 2005
[d]Budavari et al. 2001
[e]Weast 1989
[f]Boffito 2002
[g]NIOSH/OSHA 1978
[h]Perry and Chilton 1973
[i]Preisman and Davis 1948
[j]HSDB 2007
[k]Lewis 2000

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

5.1 PRODUCTION

Barium is a dense alkaline earth metal that occurs naturally in ore deposits and makes up 0.05% of the Earth's crust (Genter 2001). Barium and its compounds may be found in nature or produced industrially for various uses. The largest natural source of barium is barite ore, which is composed largely of barium sulfate and is found in beds or masses in limestone, dolomite, shales, and other sedimentary formations (Miner 1969b). The major impurities in crude barite ore are iron(III) oxide, aluminum oxide, silica, and strontium sulfate (WHO 2001). Crude barite is turned into crushed barite which not only has its own industrial uses but also serves, in turn, as the source for the production of other barium compounds. Crushed barite is first converted to barium sulfide by high-temperature, solid-phase reduction with a carbonaceous reducing agent. Barium sulfide is the starting point for the chemical manufacture of most other barium compounds (Dibello et al. 2003). One such useful compound is lithophone consisting of 28% zinc sulfide (ZnS) and 72% barium sulfate ($BaSO_4$), which is used as a white pigment in paints. Barium sulfate is produced from high-grade (75–98%) ore in association with granite and shale, crushed, and then beneficiated by washing, jigging, heavy-media separation, tabling, floatation, or magnetic separation (Stokinger 1981; USGS 2004). Barium carbonate ($BaCO_3$) occurs in nature as witherite; however, it has little economic significance due to its rareness, impurities, and almost fully depleted deposits (Kresse et al. 2007).

In 2005, the major producer of barite in the United States was from mines in Nevada. Significantly smaller amounts were produced from a single mine in Georgia. Total U.S. production for 2004 was 532,000 metric tons, a figure that represented 7.3% of world production. This production figure is 14% higher than for 2003. In 2004, 24 grinding plants within the United States produced 2,440,000 metric tons of ground or crushed (processed) barite ore. Fourteen facilities, 6 in Louisiana and 8 in Texas, produced American Petroleum Institute (API)-grade barite in 2004. These stand-alone grinding plants received barite from China and India for grinding to API specifications for the oil and gas drilling markets. Of the total production of ground and crushed barite ore in 2004, 94% (2,300,000 metric tons) was used in well drilling operations. Louisiana and Texas were the major U.S. consumers of processed barite ore (1,803,000 metric tons); much of this consumption was driven by exploration for natural gas. The demand for barite in the United States is expected to increase, while the level of drilling activity in North America remains high due to a strong demand in the United States for natural gas. The remaining 6% (142,000 metric tons) was used as filler and extenders and in the manufacture of glass and barium chemicals, such as barium sulfide (USGS 2004, 2006). A list of production and processing facilities for

barium and barium compounds in the United States along with the production or processing volume for each are provided in Tables 5-1 and 5-2 (TRI04 2006). A listing of specific manufactures of barite and barium compounds is given in Table 5-3.

5.2 IMPORT/EXPORT

For the year 2004, U.S. imports of crude barite ore totaled 1,960,000 metric tons, which was a 17% increase from levels reported in 2003. Estimates for 2005 predict a 17% increase in imports to 2,350,000 metric tons. Export volumes were at 70,000 metric tons, a 37% increase from 2003 levels. Estimates indicate a 22% increase in exports to 90,000 metric tons in 2005. Import of barium chloride, barium nitrate, and barium carbonate amounted to 130, 4,300, and 10,200 metric tons in 2004, respectively. Imports of barium oxide, hydroxide, and peroxides were reported to be 3,540 metric tons (USGS 2004, 2006).

5.3 USE

Barium and its compounds are used in oil and gas drilling muds, automotive paints, stabilizers for plastics, case hardening steels, bricks, tiles, lubricating oils, and jet fuel as well as in various types of pesticides (Bodek et al. 1988; Venugopal and Luckey 1978; WHO 2001). The largest use of mined barite, which accounts for 94% of the total output, is oil and gas well drilling (USGS 2006). The rest of barite ore (or crude barium sulfate) is utilized frequently as a colorant in paint, as a flux to reduce melting temperature in the manufacture of glass, and as a filler in plastics, rubber, and brake linings as well as in the production of other barium compounds (Dibello et al. 2003). Such barium compounds as the carbonate, chloride, and hydroxide are important in the brick, ceramic, photographic, and chemical manufacturing industries (Bodek et al. 1988).

Industrial uses of barium and its compounds are wide and varied. Barium metal and its alloys, for example, are often used as "getters" to remove gases from vacuum tubes due to their ability to absorb gases (Stokinger 1981). One of barium carbonate's major uses is as a rodenticide (Meister 2004; Worthing 1987); however, it also plays an important role in the brick, tile, ceramics, oil drilling, and chemical manufacturing industries (Dibello et al. 2003; ILO 1983). Barium sulfate, in the chemically treated, *blanc fixe* form, is used in high-quality paints as well as in glass- and papermaking (ILO 1983; Kresse et al. 2007). Barium sulfate is also added to concrete to increase the radiation shielding of this material. The chloride is used for chlorine and sodium hydroxide manufacture, as a flux for aluminum alloys, in pigment and textile dye manufacture, and in the treatment of boiler water (Dibello et al. 2003).

Table 5-1. Facilities that Produce, Process, or Use Barium

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AK	8	0	999,999	1, 5, 12, 13, 14
AL	23	0	999,999	1, 2, 3, 5, 6, 7, 8, 10, 11, 12, 13, 14
AR	10	0	49,999,999	1, 3, 5, 7, 8, 11, 12
AZ	8	0	9,999,999	1, 5, 7, 10, 13
CA	34	0	9,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CO	8	100	99,999	2, 6, 7, 8, 12, 14
CT	3	100	999,999	1, 2, 4, 6, 7, 8, 9, 12
DE	4	100,000	999,999	2, 3, 9, 13, 14
FL	2	0	999,999	1, 5, 8
GA	13	0	49,999,999	1, 2, 3, 4, 6, 7, 8, 14
IA	12	0	999,999	1, 2, 5, 7, 10, 11, 12
ID	7	10,000	999,999	1, 3, 5, 12, 13
IL	22	100	49,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
IN	19	0	9,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12
KS	13	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 13
KY	14	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9
LA	6	0	99,999	1, 5, 6, 8, 12
MA	6	1,000	99,999	1, 3, 7, 8, 11
MD	7	100	999,999	1, 2, 3, 4, 5, 6, 7, 8, 11, 12
ME	4	100	99,999	1, 5, 8, 13
MI	36	0	999,999	1, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MN	21	100	999,999	1, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14
MO	11	0	999,999	1, 3, 4, 5, 6, 7, 8, 9, 13, 14
MS	10	100	999,999	2, 3, 7, 8, 11
MT	3	10,000	99,999	1, 5, 8, 9, 12
NC	18	0	999,999	1, 2, 3, 5, 6, 7, 8, 10, 11, 12, 13
ND	1	100,000	999,999	1, 5, 9, 12
NE	14	100	9,999,999	1, 2, 3, 4, 5, 7, 8, 9, 11, 12, 13, 14
NJ	17	0	999,999	2, 3, 6, 7, 8, 10, 11
NM	6	0	49,999,999	6, 7, 8, 9, 11, 12, 14
NV	6	100	9,999,999	1, 5, 6, 7, 10, 13
NY	20	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 13
OH	54	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OK	19	0	999,999	1, 2, 3, 5, 7, 8, 11, 12, 13
OR	9	0	999,999	1, 2, 3, 5, 6, 7, 12, 13
PA	27	0	999,999	1, 2, 3, 5, 6, 7, 8, 10, 11, 12, 13
PR	2	10,000	999,999	12
RI	3	10,000	99,999	2, 3, 4, 6, 7
SC	21	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 11, 12
SD	2	100,000	999,999	1, 5, 12, 14

Table 5-1. Facilities that Produce, Process, or Use Barium

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
TN	19	100	999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
TX	46	0	9,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
UT	9	1,000	999,999	1, 2, 3, 5, 7, 8, 11, 12
VA	15	0	999,999	1, 2, 5, 6, 7, 8, 10, 12
VT	1	1,000	9,999	11
WA	3	0	999,999	2, 5, 7, 8, 12, 13, 14
WI	13	0	999,999	1, 3, 5, 6, 7, 8, 10, 11, 12, 14
WV	10	0	999,999	2, 3, 7, 8, 10, 12
WY	2	0	999	1, 2, 13

[a]Post office state abbreviations used
[b]Amounts on site reported by facilities in each state
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses
14. Process Impurity

Source: TRI04 2006 (Data are from 2004)

Table 5-2. Facilities that Produce, Process, or Use Barium Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AK	4	0	9,999,999	1, 5, 12, 14
AL	58	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
AR	47	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
AZ	41	100	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CA	89	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CO	41	0	9,999,999	1, 3, 4, 5, 6, 7, 8, 9, 12, 13, 14
CT	25	100	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13
DE	17	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13
FL	51	0	999,999	1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
GA	79	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
HI	2	1,000	99,999	1, 5, 10
IA	42	100	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ID	14	0	9,999,999	1, 2, 3, 5, 7, 8, 10, 11, 12, 13, 14
IL	136	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
IN	109	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
KS	48	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
KY	80	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
LA	56	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 13, 14
MA	42	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
MD	52	100	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
ME	25	0	99,999	1, 2, 3, 5, 7, 8, 10, 11, 12, 13
MI	125	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MN	46	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MO	68	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14
MS	39	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MT	14	100	9,999,999	1, 3, 4, 5, 6, 7, 9, 12, 13, 14
NC	77	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ND	18	0	9,999,999	1, 5, 8, 9, 12, 13, 14
NE	32	0	9,999,999	1, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13
NH	10	0	99,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 12
NJ	103	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
NM	21	0	9,999,999	1, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
NV	19	0	499,999,999	1, 2, 3, 4, 5, 7, 8, 9, 12, 13
NY	121	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OH	169	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OK	43	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OR	27	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13
PA	153	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14

Table 5-2. Facilities that Produce, Process, or Use Barium Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
PR	3	10,000	999,999	1, 2, 4, 5, 6
RI	12	100	99,999	2, 3, 4, 6, 7, 8, 11
SC	50	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
SD	7	1,000	999,999	1, 5, 7, 8, 9, 12, 13
TN	71	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
TX	114	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
UT	41	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
VA	44	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
VT	6	1,000	99,999	1, 5, 7, 8, 11
WA	26	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
WI	54	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
WV	34	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
WY	23	0	9,999,999	1, 3, 4, 5, 9, 12, 13, 14

[a]Post office state abbreviations used
[b]Amounts on site reported by facilities in each state
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses
14. Process Impurity

Source: TRI04 2006 (Data are from 2004)

Table 5-3. Current U.S. Manufacturers of Barium Metal and Selected Barium Compounds[a]

Company	Location
Barite (barium sulfate, natural):	
CIMBAR Performance Minerals	Cadet, Missouri
	Cartersville, Georgia
	Chatsworth, Georgia
Elementis Pigments, Inc.	East St. Louis, Illinois
Huber Engineered Materials Division	Quincy, Illinois
M-I, SWACO	Amelia, Louisiana
	Battle Mountain, Nevada
	Galveston, Texas
	Westlake, Louisiana
New Riverdale Ochre Company, Inc.	Cartersville, Georgia
Unimin Corporation	Plant location not specified
Barium sulfate (synthetic):	
Barium and Chemicals, Inc.	Steubenville, Ohio
CIMBAR Performance Minerals	Cartersville, Georgia
GFS Chemicals, Inc.	Columbus, Ohio
Johnson Matthey, Inc. Alfa Aesar	Ward Hill, Massachusetts
Mineral and Pigment Solutions, Inc.	South Plainfield, New Jersey
Barium acetate:	
Barium and Chemicals, Inc.	Steubenville, Ohio
Barium carbonate:	
Barium and Chemicals, Inc.	Steubenville, Ohio
CERAC, Inc.	Milwaukee, Wisconsin
Chemical Products Corporation	Cartersville, Georgia
Johnson Matthey, Inc. Alfa Aesar	Ward Hill, Massachusetts
Mallinckrodt Inc. Pharmaceuticals Group	St. Louis, Missouri
Osram Sylvania Inc.	Towanda, Pennsylvania
Barium chloride:	
Barium and Chemicals, Inc.	Steubenville, Ohio
Chemical Products Corporation	Cartersville, Georgia
GFS Chemical, Inc.	Columbus, Ohio
Johnson Matthey, Inc. Alfa Aesar	Ward Hill, Massachusetts
Mallinckrodt Inc. Pharmaceuticals Group	St. Louis, Missouri
Osram Sylvania Inc.	Towanda, Pennsylvania
Barium hydroxide:	
Barium and Chemicals, Inc.[b,c,d]	Steubenville, Ohio
Johnson Matthey, Inc. Alfa Aesar[b,c]	Ward Hill, Massachusetts
Mallinckrodt, Inc. Pharmaceuticals Group[e]	St. Louis, Missouri
Barium oxide:	
Barium and Chemicals, Inc.	Steubenville, Ohio

Table 5-3. Current U.S. Manufacturers of Barium Metal and Selected Barium Compounds[a]

Company	Location
Barium sulfide:	
Barium and Chemicals, Inc.	Steubenville, Ohio
Chemical Products Corporation	Cartersville, Georgia
Johnson Matthey, Inc. Alfa Aesar	Ward Hill, Massachusetts

[a]Derived from SRI 2006 unless otherwise noted. SRI reports production of chemicals produced in commercial quantities (defined as exceeding 5,000 pounds or $10,000 in value annually) by the companies listed.
[b]Barium hydroxide, anhydrous [$Ba(OH)_2$]
[c]Barium hydroxide octahydrate [$Ba(OH)_2 \cdot 8H_2O$]
[d]Barium hydroxide monohydrate [$Ba(OH)_2 \cdot H_2O$]
[e]Barium hydroxide, hydration not specified

Barium oxide is used to dry gases and solvents, strengthen ceramics, and as a component in some specialty cements. Barium hydroxide plays a role in glass manufacturing, synthetic rubber vulcanization, in the production of barium greases and plasticizers, as a component in sealants, pigment dispersion, paper manufacturing, sugar refining, in animal and vegetable oil refining, and in the protection of objects made of limestone from deterioration. Barium acetate is used in printing fabrics, in lubricating grease, and as a catalyst for organic reactions. Finally, the main function of barium sulfide is to act as a starting point for the production of a number of other barium compounds (Dibello et al. 2003; ILO 1983). This compound is also used in the production of thin-film electroluminescent phosphors and the vulcanization of carbon black-filled neoprene rubbers.

Barium and its compounds have several important medical uses as well. Barium chloride was formerly used in treating complete heart block, because periods of marked bradycardia and asystole were prevented through its use. This use was abandoned, however, mainly due to barium chloride's toxicity (Hayes 1982). Characterized by extreme insolubility, chemically pure barium sulfate is non toxic to humans. It is frequently utilized as a benign, radiopaque aid to x-ray diagnosis in colorectal and some upper gastrointestinal examinations, because it is normally not absorbed by the body after oral intake (de Zwart et al. 2001; Doull et al. 1980; ILO 1983; Lin 1996; Newman 1998; Pijl et al. 2002; Rae 1977).

5.4 DISPOSAL

In case of a spill, it is suggested that persons not wearing protective equipment be restricted from the area. Furthermore, ventilation should be provided in the room and the spilled material collected in as safe a manner as possible. Persons in charge of vessels or facilities are required to notify the National Response Center (NRC) immediately, when there is a release of this designated hazardous substance, in an amount equal to or greater than its reportable quantity of 1,000 pounds or 454 kg (HSDB 2007). Barium compounds (particularly soluble ones) should be placed in sealed containers and reclaimed or disposed of in a secured sanitary landfill (IPCS 1991; NIOSH/OSHA 1978). It is also suggested that all federal, state, and local regulations concerning barium disposal should be followed (HSDB 2007). No other guidelines or regulations concerning disposal of barium and its compounds were found.

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6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

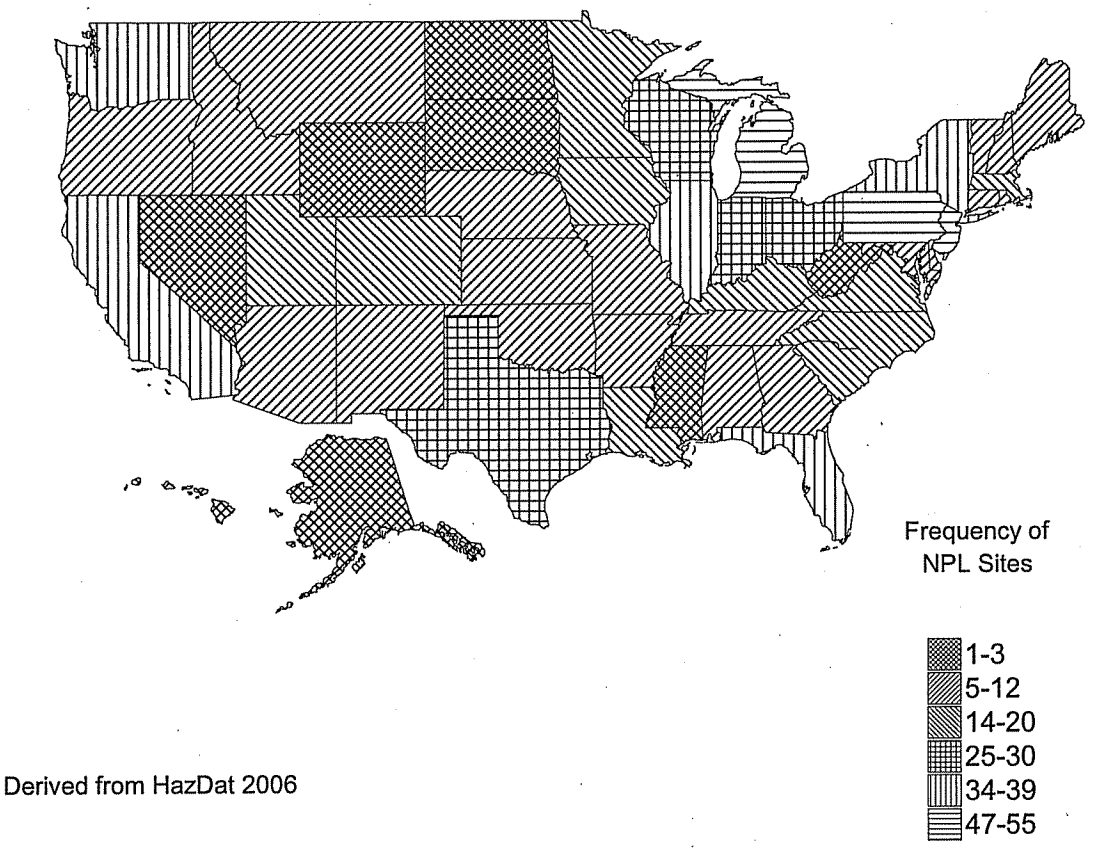
Barium has been identified in at least 798 of the 1,684 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2006). However, the number of sites evaluated for barium is not known. The frequency of these sites can be seen in Figure 6-1. Of these sites, 794 are located within the United States, 1 is in the Territory of Guam, and 3 are located in the Commonwealth of Puerto Rico (the Territory of Guam and the Commonwealth of Puerto Rico are not shown).

Barium is a naturally occurring component of minerals that are found in small but widely distributed amounts in the earth's crust, especially in igneous rocks, sandstone, shale, and coal (Kunesh 1978; Miner 1969a). Barium enters the environment naturally through the weathering of rocks and minerals. Anthropogenic releases are primarily associated with industrial processes. Barium is present in the atmosphere, urban and rural surface water, soils, and many foods.

Under natural conditions, barium is stable in the +2 valence state and is found primarily in the form of inorganic complexes. Conditions such as pH, Eh (oxidation-reduction potential), cation exchange capacity, and the presence of sulfate, carbonate, and metal oxides (e.g., oxides of aluminum, manganese, silicon, and titanium) will affect the partitioning of barium and its compounds in the environment. The major features of the biogeochemical cycle of barium include wet and dry deposition to land and surface water, leaching from geological formations to groundwater, adsorption to soil and sediment particulates, and biomagnification in terrestrial and aquatic food chains.

The general population is exposed to barium through consumption of drinking water and foods, usually at low levels. Workers in barium mining or processing industries and individuals who reside near such industries might be exposed to relatively high levels, primarily through the inhalation of fugitive dust containing barium compounds. The most recent occupational exposure estimates indicate that about 10,000 people were potentially exposed to barium and about 474,000 to barium compounds in workplace environments in the United States in 1980 (NIOSH 1989a).

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



Derived from HazDat 2006

6.2 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005d). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ 10 or more full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005d).

Barium is a highly reactive metal that occurs naturally only in a combined state. The element is released to environmental media by both natural processes and anthropogenic sources.

According to the SARA Section 313 Toxics Release Inventory (TRI), an estimated total of 230 million pounds (105,000 metric tons) of barium and barium compounds were released to the environment from manufacturing and processing facilities in the United States in 2004 (TRI04 2006) (see Tables 6-1 and 6-2). Most of these barium releases were to land. The TRI data must be viewed with caution since only certain types of facilities were required to report. This is not an exhaustive list.

6.2.1 Air

Estimated combined releases of 2.51 million pounds (1,140 metric tons) of barium (0.35 million pounds) and barium compounds (2.16 million pounds) to the atmosphere from 1,107 domestic manufacturing and processing facilities in 2004, accounted for about 1.09% of the estimated total environmental releases from facilities required to report to the TRI (TRI04 2006). These releases are summarized in Tables 6-1 and 6-2.

Barium is released primarily to the atmosphere as a result of industrial emissions during the mining, refining, and production of barium and barium chemicals, fossil fuel combustion (Miner 1969a), and

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Barium[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AK	3	24,620	0	0	306,812	0	146,620	184,812	331,432
AL	5	6,963	504	0	39,889	4,748	7,459	44,645	52,104
AZ	2	1,062	0	0	1,950,946	0	1,823,807	128,201	1,952,008
CA	2	1,911	0	0	797,507	78	799,418	78	799,496
CO	1	0	0	No data	0	0	No data	0	0
CT	1	4	4	0	0	3,515	4	3,519	3,523
DE	1	20	64	0	0	0	84	0	84
GA	4	81	0	0	3,757	0	81	3,757	3,837
IA	4	36,228	0	0	163	0	36,228	163	36,391
ID	1	14	0	0	130,611	0	130,625	0	130,625
IL	3	9,428	61	0	45,553	0	9,489	45,553	55,042
IN	2	10	255	0	18,074	16,900	10	35,229	35,239
KS	2	7,501	0	0	161,964	526,878	169,465	526,878	696,343
KY	2	75,258	0	0	0	0	75,258	0	75,258
MI	5	230	666	0	44,245	271,175	896	315,420	316,316
MN	2	114,719	0	0	694	0	114,719	694	115,413
MO	1	0	0	0	0	81	0	81	81
NC	3	11	0	0	1,559	0	11	1,559	1,570
NE	6	23,979	3,320	0	37,786	362,667	65,080	362,672	427,752
NJ	2	89	0	0	30	272	89	302	391
NM	1	0	0	0	0	0	0	0	0
NV	2	1,243	0	0	817,749	0	818,992	0	818,992
NY	5	35,001	137	0	3,073	15,991	35,140	19,062	54,202
OH	14	866	372	16,649	287,615	6,472	220,822	91,152	311,974
OK	1	1,906	5	0	250	0	1,906	255	2,161
OR	1	0	0	0	230,293	1	230,293	1	230,294
PA	4	756	0	0	344,131	51,746	322,501	74,132	396,633
SC	2	253	0	0	0	72	253	72	325
SD	1	500	0	0	39,480	0	39,980	0	39,980
TN	1	0	0	No data	0	0	No data	0	0
TX	9	7,392	4,029	0	71,083	7	81,473	1,038	82,511
UT	2	10	0	0	31,035	0	31,010	35	31,045
VA	2	0	1,900	0	111,900	0	95,900	17,900	113,800
WI	1	0	0	0	257,400	0	0	257,400	257,400

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Barium[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
WV	2	4,214	10	0	77,821	201	82,045	202	82,246
Total	100	354,269	11,327	16,649	5,811,421	1,260,803	5,339,658	2,114,811	7,454,470

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other on-site landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI04 2006 (Data are from 2004)

Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Barium Compounds[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AK	1	16,122	0	0	16,122	0	32,244	0	32,244
AL	34	69,621	94,049	3,900	11,966,847	67,278	12,062,542	139,153	12,201,695
AR	16	28,134	107,680	0	2,906,741	44,565	3,038,693	48,427	3,087,120
AZ	10	11,779	0	0	3,951,882	61	3,962,437	1,285	3,963,722
CA	14	8,998	514	0	56,003	3,624	20,826	48,313	69,139
CO	18	14,440	2,232	0	8,687,234	7,500	5,019,424	3,691,982	8,711,406
CT	4	505	5	0	66,963	22,315	540	89,248	89,788
DE	3	17,256	9,034	0	480,594	121,025	486,290	141,619	627,909
FL	22	49,588	9,750	0	2,232,733	216,852	2,134,494	374,429	2,508,924
GA	29	61,732	112,867	0	8,660,091	19,737	8,798,097	56,330	8,854,427
HI	1	45	0	0	29,331	0	45	29,331	29,376
IA	24	142,028	3,709	0	4,358,835	229,865	3,293,915	1,440,522	4,734,437
ID	6	8,334	11,400	0	137,167	83	98,901	58,083	156,984
IL	56	218,005	114,459	0	13,593,791	370,276	6,061,909	8,234,621	14,296,530
IN	45	72,823	31,471	0	8,274,849	82,196	7,095,068	1,366,271	8,461,340
KS	12	78,277	938	0	4,774,271	250	4,853,486	250	4,853,736
KY	38	49,663	76,268	0	7,134,938	211,117	5,405,100	2,066,886	7,471,986
LA	17	70,200	40,931	1,367	4,315,727	8,307	4,411,344	25,188	4,436,532
MA	14	2,275	1,283	0	257,892	21,982	20,043	263,389	283,432
MD	18	9,340	1,880	59	468,562	697,038	90,155	1,086,724	1,176,879
ME	6	1,301	4,100	0	81,692	0	71,193	15,900	87,093
MI	32	55,968	125,134	56	10,513,385	24,961	7,965,087	2,754,417	10,719,504
MN	22	48,772	22,540	0	8,233,091	71,522	7,430,251	945,673	8,375,924
MO	30	231,257	11,722	0	10,226,716	731	10,356,850	113,576	10,470,426
MS	16	5,973	14,703	0	1,626,877	528	1,627,878	20,203	1,648,081
MT	6	111,530	781	0	8,892,216	175,814	8,951,015	229,325	9,180,340
NC	31	30,632	68,807	0	3,082,682	171,007	2,921,804	431,324	3,353,127
ND	9	39,926	24,052	0	13,826,846	6,786	7,126,843	6,770,767	13,897,610
NE	11	37,560	52	0	3,982,921	6,350	3,739,570	287,313	4,026,883
NH	5	1,532	0	0	26,500	1,583	9,632	19,983	29,615
NJ	20	7,826	9,949	0	96,325	297,053	7,832	403,321	411,153
NM	6	13,400	250	0	5,210,450	750	5,204,409	20,441	5,224,850
NV	4	25,974	0	0	1,432,649	37	1,458,623	37	1,458,660
NY	24	18,085	136,769	0	1,454,199	311,766	790,432	1,130,387	1,920,819
OH	94	43,103	82,835	319	8,642,836	424,109	5,383,148	3,810,054	9,193,202
OK	12	25,481	11,600	0	2,005,538	19	1,737,944	304,694	2,042,638
OR	5	12,393	2,120	0	115,146	0	100,513	29,146	129,659

Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Barium Compounds[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
PA	72	50,576	40,857	250	3,948,212	422,230	1,469,982	2,992,143	4,462,125
PR	1	1,542	0	0	91	0	1,633	0	1,633
RI	3	5	23	0	1,072	477	28	1,549	1,577
SC	36	27,220	51,763	0	1,313,342	678,479	1,263,992	806,812	2,070,803
SD	2	1,057	36	0	731,856	0	681,949	51,000	732,949
TN	24	64,154	106,884	0	4,653,790	334	4,240,684	584,478	4,825,162
TX	48	158,316	67,044	0	16,122,300	3,011,576	16,164,215	3,195,022	19,359,236
UT	9	5,422	100	0	3,661,314	3,902	3,510,292	160,446	3,670,738
VA	28	25,919	26,448	0	2,006,961	189,025	1,704,517	543,836	2,248,353
VT	1	250	5	0	0	28,667	250	28,672	28,922
WA	11	1,318	3,118	0	2,274,705	42	2,119,156	160,027	2,279,183
WI	30	37,077	20,145	0	890,567	1,023,144	342,849	1,628,084	1,970,933
WV	20	75,248	18,436	0	5,243,526	78,000	4,479,752	935,458	5,415,210
WY	7	68,528	3,229	0	7,343,092	0	6,751,399	663,450	7,414,849
Total	1,007	2,156,511	1,471,972	5,951	210,011,467	9,052,963	174,499,278	48,199,586	222,698,864

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other on-site landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI04 2006 (Data are from 2004)

entrainment of soil and rock dust into the air (Schroeder 1970). In addition, coal ash, containing widely variable amounts of barium, is also a source of airborne barium particulates (Miner 1969a; Schroeder 1970). In 1969, an estimated 18% of the total U.S. barium emissions to the atmosphere resulted from the processing of barite ore, and more than 28% of the total was estimated to be from the production of barium chemicals. The manufacture of various end products (e.g., drilling well muds, and glass, paint, and rubber products) and the combustion of coal were estimated to account for an additional 23 and 26% of the total barium emissions for 1969, respectively (Davis 1972).

Estimates of barium releases from individual industrial processes are available for particulate emissions from the drying and calcining of barium compounds and for fugitive dust emissions during the processing of barite ore. Soluble barium compounds (unspecified) are emitted as particulates from barium chemical dryers and calciners to the atmosphere during the processing of barium carbonate, barium chloride, and barium hydroxide (Reznik and Toy 1978). Uncontrolled particulate emissions of soluble barium compounds from chemical dryers and calciners during barium processing operations may range from 0.04 to 10 g/kg of final product. Controlled particulate emissions are less than 0.25 g/kg of final product. Based on an uncontrolled emission factor of 5 g/kg and a controlled emission factor of 0.25 g/kg, total particulate emissions from the drying and calcining of barium carbonate, barium chloride, and barium hydroxide are estimated to be 160 metric tons (352,800 pounds) per year (Reznik and Toy 1978).

Fugitive dust emissions occur during processing (grinding and mixing) of barite ore and may also occur during the loading of bulk product of various barium compounds into railroad hopper cars (Reznik and Toy 1978). Based on an emission factor of 1 g/kg, total emissions of fugitive dust from the domestic barium chemicals industry during the grinding of barite ore have been estimated to be approximately 90 metric tons (198,450 pounds) per year (Reznik and Toy 1978). Other particulate emissions from the industrial production of barium compounds include an estimated 820 metric tons (1.8 million pounds) per year from uncontrolled kilns during the processing of barite ore and 8 metric tons (17,640 pounds) per year from black ash (i.e., barium sulfide) rotary kilns during the production of barium hydroxide (Reznik and Toy 1978). Electric utilities that burn bituminous coal emit a small fraction of the barium contained in coal into the air. For example, it is estimated that 830 pounds/year of barium are released to air from a 650 megawatt (MW) plant, in comparison to 270,000 pounds/year released as ash to land-based waste sites (Rubin 1999).

The use of barium in the form of organometallic compounds as a smoke suppressant in diesel fuels results in the release of solids to the atmosphere (Miner 1969a; Ng and Patterson 1982; Schroeder 1970). The

maximum concentration of soluble barium in exhaust gases containing barium-based smoke suppressants released from test diesel engines and operating diesel vehicles is estimated to be 12,000 μg/m^3, when the barium concentration in the diesel fuel is 0.075% by weight and 25% of the exhausted barium (at a sampling point 10 feet from the engine and upstream from the muffler) is soluble (Golothan 1967). Thus, 1 L of this exhaust gas contains an estimated 12 μg soluble barium or 48 μg total barium (Schroeder 1970). However, recent legislation requiring the use of low-sulfur fuel in diesel engines has eliminated the need for barium as a sulfur-scavenging additive and, therefore, has greatly reduced the emissions of barium from diesel engine exhaust (Schauer et al. 1999; Winkler 2002).

6.2.2 Water

Estimated combined releases of 1.48 million pounds (674 metric tons) of barium (0.01 million pounds) and barium compounds (1.47 million pounds) to surface water from 1,107 domestic manufacturing and processing facilities in 2004, accounted for about 0.64% of the estimated total environmental releases from facilities required to report to the TRI (TRI04 2006).

The primary source of naturally occurring barium in drinking water results from the leaching and eroding of sedimentary rocks into groundwater (Kojola et al. 1978). Although barium occurs naturally in most surface water bodies (i.e., approximately 99% of those examined) (DOI 1970), releases of barium to surface waters from natural sources are much lower than those to groundwater (Kojola et al. 1978).

About 80% of the barium produced is used as barite to make high-density oil and gas well drilling muds, and during offshore drilling operations there are periodic discharges of drilling wastes in the form of cuttings and muds into the ocean (Ng and Patterson 1982). For example, in the Santa Barbara Channel region, about 10% of the muds used are lost into the ocean (Ng and Patterson 1982). Operations involving three drilling platforms in the Santa Maria Basin off the coast of central California released approximately 1.8×10^6 kg of barium to the ocean in discharged muds, cuttings, and waste water from 1986 to 1994 (Phillips et al. 1998). The use of barium in offshore drilling operations may increase barium pollution, especially in coastal sediments (Ng and Patterson 1982).

6.2.3 Soil

Estimated combined releases of 216 million pounds (98,095 metric tons) of barium (5.81 million pounds) and barium compounds (210 million pounds) to soils from 1,107 domestic manufacturing and processing facilities in 2004, accounted for about 93.7% of the estimated total environmental releases from facilities

required to report to the TRI (TRI04 2006). An additional combined total of 0.023 million pounds (10 metric tons) from barium (0.017 million pounds) and barium compounds (0.006 million pounds), constituting about 0.01% of the total environmental emissions, were released via underground injection (TRI04 2006). These releases are summarized in Tables 6-1 and 6-2.

The process of drilling for crude oil and natural gas generates waste drilling fluids or muds, which are often disposed of by land farming. Most of these fluids are water based and contain barite and other metal salts. Thus, barium may be introduced into soils as the result of land farming these slurried reserve pit wastes (Bates 1988).

The use of barium fluorosilicate and carbonate as insecticides (Beliles 1979; Meister 2004) might also contribute to the presence of barium in agricultural soils.

Barium has been detected with a positive geometric mean concentration of 100.5 ppm in soil samples from approximately 52% of the hazardous waste sites that have had samples analyzed by the CLP (CLPSD 1989). Note that these data from the CLPSD represent frequency of occurrence and concentration data for NPL sites only.

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

Most barium released to the environment from industrial sources is in forms that do not become widely dispersed (Ng and Patterson 1982). In the atmosphere, barium is likely to be present in particulate form (EPA 1984). Although chemical reactions may cause changes in speciation of barium in air, the main mechanisms for the removal of barium compounds from the atmosphere are likely to be wet and dry deposition (EPA 1984).

In aquatic media, barium is likely to precipitate out of solution as an insoluble salt (i.e., as $BaSO_4$ or $BaCO_3$). Waterborne barium may also adsorb to suspended particulate matter through the formation of ion pairs with natural anions such as bicarbonate or sulfate in the matter (Bodek et al. 1988; EPA 1984; Giusti et al. 1993; Lagas et al. 1984; Tanizaki et al. 1992). Precipitation of barium sulfate salts is accelerated when rivers enter the ocean because of the high sulfate content (905 mg/L) in the ocean (Bowen 1966; WHO 2001). It is estimated that only 0.006% of the total barium input into oceans from freshwater sources remains in solution (Chow et al. 1978; WHO 2001). Sedimentation of suspended

solids removes a large portion of the barium content from surface waters (Benes et al. 1983). There is evidence to suggest that the precipitation of barium from the surface of fresh and marine waters occurs, in part, as the result of the barite crystal formation in microorganisms (González-Muñoz et al. 2003). Barium in sediments is found largely in the form of barium sulfate (barite). Coarse silt sediment in a turbulent environment will often grind and cleave the barium sulfate from the sediment particles leaving a buildup of dense barites (Merefield 1987). Estimated soil:water distribution coefficients (Kd) (i.e., the ratio of the quantity of barium sorbed per gram of sorbent to the concentration of barium remaining in solution at equilibrium) range from 200 to 2,800 for sediments and sandy loam soils (DOE 1984; Rai et al. 1984).

The uptake of barium by fish and marine organisms is also an important removal mechanism (Bowen 1966; Schroeder 1970). Barium levels in sea water range from 2 to 63 µg/L with a mean concentration of about 13 µg/L (Bowen 1979). Barium was found to bioconcentrate in marine plants by a factor of 400–4,000 times the level present in the water (Bowen 1966). Bioconcentration factors in marine animals, plankton, and brown algae of 100, 120, and 260, respectively, have been reported (Schroeder 1970). In freshwater, a bioconcentration factor of 129 was estimated in fish where the barium in water was 0.07 mg/L (Hope et al. 1996).

Barium added to soils (e.g., from the land farming of waste drilling muds) may either be taken up by vegetation or transported through soil with precipitation (Bates 1988). Relative to the amount of barium found in soils, little is typically bioconcentrated by plants (Schroeder 1970). For example, a bioconcentration factor of 0.4 has been estimated for plants in a Virginia floodplain with a barium soil concentration of 104.2 mg/kg (Hope et al. 1996). However, there are some plants, such as legumes, forage plants, Brazil nuts, and mushrooms that accumulate barium (Aruguete et al. 1998; IPCS 1991; WHO 2001). Bioconcentration factors from 2 to 20 have been reported for tomatoes and soybeans (WHO 2001).

Barium is not very mobile in most soil systems, due to the formation of water-insoluble salts and an inability of the barium ion to form soluble complexes with fulvic and humic acids (WHO 2001). The rate of transportation of barium in soil is dependent on the characteristics of the soil material. Soil properties that influence the transportation of barium to groundwater are cation exchange capacity, calcium carbonate ($CaCO_3$) content and pH. In soil with a high cation exchange capacity (e.g., fine textured mineral soils or soils with high organic matter content), barium mobility will be limited by adsorption (Bates 1988; Kabata-Pendias and Pendias 1984). High $CaCO_3$ content limits mobility by precipitation of

the element as $BaCO_3$ (Lagas et al. 1984). Barium will also precipitate as barium sulfate in the presence of sulfate ions (Bodek et al. 1988; Lagas et al. 1984). Barium is more mobile and is more likely to be leached from soils in the presence of chloride due to the high solubility of barium chloride as compared to other chemical forms of barium (Bates 1988; Lagas et al. 1984). Barium may become more mobile in soils under acid conditions as barium in water-insoluble salts, such as barium sulfate and carbonate, becomes more soluble (WHO 2001). Barium complexes with fatty acids (e.g., in acidic landfill leachate) will be much more mobile in the soil due to the lower charge of these complexes and subsequent reduction in adsorption capacity (Lagas et al. 1984).

Barium mobility in soil is reduced by the precipitation of barium carbonate and sulfate. Humic and fulvic acid have not been found to increase the mobility of barium (EPA 1984).

6.3.2 Transformation and Degradation

6.3.2.1 Air

Elemental barium undergoes oxidation in air and is oxidized readily in moist air (Boffito 2002; EPA 1983; Kresse et al. 2007; Kunesh 1978). The residence time of barium in the atmosphere may be several days, depending on the size of the particulate formed, the chemical nature of the particulate, and environmental factors such as rainfall (EPA 1984; WHO 2001).

6.3.2.2 Water

Under natural conditions, barium will form compounds in the +2 oxidation state. Barium does not hydrolyze appreciably except in highly alkaline environments (i.e., at pH levels ≥10) (Bodek et al. 1988).

Appreciable levels of barium sulfate occur because natural water often contains high sulfate concentrations, especially ocean water. Since the solubility of barium sulfate is low, only trace amounts of barium dissolve in surface water (Bodek et al. 1988; NAS 1977). At pH levels of 9.3 or below, barium sulfate may limit barium concentrations in natural waters (Bodek et al. 1988). The solubility of barium sulfate increases considerably in the presence of chloride (Cl^-) and other anions (e.g., NO_3^- and CO_3^{-2}), and at pH levels of 9.3 or below, the barium ion (Ba^{2+}) is the dominant species (Bodek et al. 1988; NAS 1977). The Ba^{2+} ion is stable under the pH-Eh range of natural systems. However, natural and treated waters usually contain sufficient sulfate so that a barium ion concentration of more than 1,000–

1,500 µg/L cannot be maintained in solution (EPA 1983; Hem 1959; Lagas et al. 1984; McCabe et al. 1970).

As pH levels increase above 9.3 and in the presence of carbonate, barium carbonate becomes the dominant species (Bodek et al. 1988; Singer 1974). Barium carbonate also exhibits fast precipitation kinetics and very low solubility and in alkaline environments limits the soluble barium concentration (Faust and Aly 1981; Hem 1959; Rai et al. 1984; Singer 1974). Barium forms salts of low solubility with arsenate, chromate, fluoride, oxalate, and phosphate ions (Bodek et al. 1988; EPA 1983; Kunesh 1978). The chloride, hydroxide, and nitrate of barium are water-soluble (Bodek et al. 1988; EPA 1983; Kirkpatrick 1978) and are frequently detected in aqueous environments (Rai et al. 1984).

Barium also forms complexes with natural organics in water (e.g., fatty acids in acidic landfill leachates) to a limited extent (Lagas et al. 1984; Morel 1983; Rai et al. 1984).

6.3.2.3 Sediment and Soil

Barium reacts with metal oxides and hydroxides in soil and is subsequently adsorbed onto soil particulates (Hem 1959; Rai et al. 1984). Adsorption onto metal oxides in soils and sediments probably acts as a control over the concentration of barium in natural waters (Bodek et al. 1988). Under typical environmental conditions, barium displaces other adsorbed alkaline earth metals from MnO_2, SiO_2, and TiO_2 (Rai et al. 1984). However, barium is displaced from Al_2O_3 by other alkaline earth metals (Rai et al. 1984). The ionic radius of the barium 2+ ion, its typical oxidation state, makes isomorphous substitution possible only with strontium, and generally not with the other members of the alkaline earth elements (Kirkpatrick 1978). Among the other elements that occur with barium in nature, substitution is common only with potassium but not with the smaller ions of sodium, iron, manganese, aluminum, and silicon (Kirkpatrick 1978).

Barium is also adsorbed onto soil and subsoil through electrostatic interactions (Bodek et al. 1988; Singer 1974). The cation exchange capacity of the sorbent largely controls the retention of barium in soils (Bodek et al. 1988). Barium is strongly adsorbed by clay minerals (Kabata-Pendias and Pendias 1984; Lagas et al. 1984).

Barium can also form salts with acetate, nitrate, chloride, and hydroxide ions in soil. The mobility of barium in soils increases upon formation of these water soluble salts (Bodek et al. 1988). In general, the solubility of barium compounds increases with decreasing pH.

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to barium depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of barium in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on barium levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable. The analytical methods available for monitoring barium in a variety of environmental media are detailed in Chapter 7.

6.4.1 Air

The concentration of barium in ambient air is estimated to be <0.05 μg/m^3 (IPCS 1991). Airborne barium likely exists as the carbonate or sulfate salts and is carried on particulate matter that results as a consequence of natural processes (e.g., suspension of soil dust) or anthropogenic activities (e.g., combustion process, mining and calcining of barium ores) (WHO 2001). However, there is no apparent correlation between the degree of industrialization and barium concentrations in ambient air (Winkler 2002). Particulate matter from diesel exhaust was once a source of barium in ambient air. However, barium emissions from diesel engines has been greatly diminished to near zero emissions with the current use of low-sulfur diesel fuels, which do not require the addition of barium as a sulfur-scavenging agent (Hildemann et al. 1991; Schauer et al. 1999; Shahin et al. 2000; Winkler 2002).

Tabor and Warren (1958) report urban and suburban air concentrations of barium ranging from <0.005 to 1.5 μg/m^3. In another study of barium concentrations in ambient air, values ranged from 0.0015 to 0.95 mg/m^3 (EPA 1984). No distinct pattern related to industrialization appeared in the results reported on 754 samples from 18 cities and four suburban areas in the United States. For example, in Houston, Texas and its suburbs, 76% of the samples contained barium at levels ranging from 0.005 to 1.5 μg/m^3, whereas in Fort Worth, Texas, 66% of the samples had values <0.005 μg/m^3 (Tabor and Warren 1958).

Another compilation of atmospheric data shows barium concentrations in urban atmospheres of North America ranging from $2x10^{-4}$ to $2.8x10^{-2}$ μg/m^3 with a mean concentration of $1.2x10^{-2}$ μg/m^3 (Bowen

1979). In contrast, barium levels in samples from the South Pole and northern Norway were $1.6x10^{-5}$ and $7.3x19^{-4}$ μg/m^3, respectively (Bowen 1979). Mean barium concentrations in background air collected between April and October 2002 on the campus of the University of Birmingham, United Kingdom, were 0.32 and 1.4 ng/m^3 in the <0.5 and 3.0–7.2 μm particular matter fractions, respectively (Birmili et al. 2006).

Maximum ground-level barium concentrations (as soluble compounds) associated with uncontrolled atmospheric particulate emissions from chemical dryers and calciners at barium-processing plants have been estimated (using dispersion modeling) to range from 1.3 to 330 μg/m^3 over a 24-hour averaging time at locations along facility boundaries (i.e., away from the source of emission) (Reznik and Toy 1978).

Barium has been measured in dust samples taken from 49 residences in Ottawa, Canada. Mean and median concentrations of 405.56 and 222.22 mg barium/kg dust, respectively, were measured within a sub-fraction of the dust samples where the particulate sizes ranged from 100 to 250 μm (Butte and Heinzow 2002; Rasmussen et al. 2001).

Barium has been measured in rain and snow collected near Claremont, New Hampshire in 1996–1997 (Feng et al. 2000). Barium concentrations in rain ranged from 0.22 to 0.84 μg/L with a mean concentration of 0.39 μg/L. In snow, barium concentrations ranged from 0.64 to 7.44 μg/L with a mean concentration of 1.5 μg/L.

Barium has been detected in air samples collected at 24 of the 798 hazardous waste sites where barium has been detected in some environmental medium (HazDat 2006). The HazDat information includes data from both NPL and other Superfund sites. Concentrations of barium in air ranged from 0.015 to 327,000,000 μg/m^3 in 16 onsite (HazDat 2006). In comparison, concentrations of barium in air ranged from 0.0135 to 561,000,000 μg/m^3 in 12 offsite samples (HazDat 2006).

6.4.2 Water

Barium has been found in almost all raw surface waters and public drinking water supplies sampled (i.e., approximately 99%) (Kopp 1969) at concentrations ranging from ≤5 to 15,000 μg/L with mean concentrations generally on the order of 10–60 μg/L (Barnett et al. 1969; Bowen 1979; DOI 1970; Durfor and Becker 1964; Durum and Haffty 1961; Elinder and Zenz 1994; EPA 2005c; Kopp 1969; Longerich et al. 1991; McCabe et al. 1970; Neal et al. 1996; Saleh and Wilson 1999; Tuovinen et al. 1980). Barium

concentrations are lowest (mean value of 15 µg/L) in the drainage basins of the western Great Lakes and highest (mean value of 90 µg/L) in the southwestern drainage basins of the lower Mississippi Valley (EPA 2005c). Barium concentrations in the shallow aquifer below Denver, Colorado, have been reported to range from 18 to 594 µg/L with a median value of 104 µg/L (Bruce and McMahon 1996). Barium concentrations in most drinking water supplies are <200 µg/L with a mean concentration of 28.6 µg/L (EPA 2005c). In California, mean and median values of 302 and 160 µg/L, respectively, were measured for barium concentrations in drinking water supplies (Storm 1994).

Barium concentrations in groundwater supplies have been known to exceed EPA's maximum contaminant level (MCL) of 2.0 mg/L (2,000 µg/L) (EPA 2002a); this may be due to leaching and erosion of barium from sedimentary rocks (Calabrese 1977; Kojola et al. 1978). For example, community water supplies from deep rock and drift wells in northeastern Illinois have been found to have barium concentrations ranging from 1,100 to 10,000 µg/L (Calabrese 1977). Many communities in Kentucky, Pennsylvania, and New Mexico have drinking water where the barium content is up to ten times higher than the MCL (EPA 2005c). Water samples taken from groundwater wells in Texas that are within 750 m of brine injection, dry, or plugged gas/oil wells contain barium ranging in concentration from 1.2 to 2,300 µg/L (Hudak and Wachal 2001).

A mean concentration of 167 µg/L for barium was measured in influent streams of a public waste water treatment plant in Melbourne, Australia (Wilkie et al. 1996). The amount of barium in the influent streams could not be accounted for based on the mean concentrations of barium in domestic water supplies (20 µg/L) or domestic sewage (38 µg/L). Instead, it is likely that the barium unaccounted for in the influent stream is the result of barium carried in effluents from industries that are discharged into the catchment area of the treatment plant.

Barium has also been found in sea water at concentrations ranging from 2 to 63 µg/L with a mean concentration of 13 µg/L (Bowen 1979).

Barium has been detected in surface water and groundwater samples collected at 257 and 561 of the 798 hazardous waste sites, respectively, where barium has been detected in some environmental medium (HazDat 2006). The HazDat information includes data from both NPL and other Superfund sites. Maximum concentrations of barium in surface water (lakes, streams, ponds, etc.) ranged from 0.33 to 18,100,000 µg/L in 77 onsite samples (HazDat 2006). In comparison, maximum concentrations of barium in surface water (lakes, streams, ponds, etc.) ranged from 10 to 73,8000 µg/L in 112 offsite

samples (HazDat 2006). The maximum concentrations of barium in groundwater ranged from 0.064 to 2,100,000 µg/L in 442 onsite samples (HazDat 2006). In comparison, maximum concentrations of barium in groundwater ranged from 0.05 to 803,000 µg/L in 260 offsite samples (HazDat 2006).

6.4.3 Sediment and Soil

Barium is relatively abundant in the earth's crust and is found in most soils at concentrations (Table 6-3) ranging from about 15 to 3,500 ppm (dry weight) and mean values ranging between 265 and 835 ppm, depending on soil type (EPA 1995a; Kabata-Pendias and Pendias 1984; Lide 2005; Zenz et al. 1994). The barium content in cultivated and uncultivated soil samples collected during a number of field studies ranged from 15 to 1,000 ppm (mean concentration of 300 ppm) for B horizon soils (subsurface soils) in the eastern United States and from 70 to 5,000 ppm (mean concentration of 560 ppm) for B horizon soils in the western United States (Bowen 1979; Schroeder 1970; Shacklette and Boerngen 1984). Barium content ranged from 150 to 1,500 ppm for surface horizon soils collected in Colorado (mean concentration of 550 ppm) (Connor and Shacklette 1975). Soil samples (0–6 inch depth) taken from three New England cities, Boston, Providence and Springfield, were reported to have mean barium concentrations of 53.95, 45.29 and 45.17 mg/kg, respectively, and upper 95% interval values of 66.25, 59.43, and 51.03 mg/kg, respectively (Bradley et al. 1994). Soil samples were obtained from areas that were not influenced by industrial activity, such as along roads and sidewalks, parks and open lots, and may account for why the mean values for barium concentration were well below a mean value of 420 mg/kg for the United States.

Geometric mean concentrations of barium in sediments taken from 16 sampling sites along the southern shore of Lake Ontario and southeastern shore of Lake Erie ranged from 6.0 to 143.6 µg/g (dry weight) (Lowe and Day 2002). Thirteen of the 16 sites had mean barium concentrations that exceeded EPA's guidelines (20–60 µg barium/g dry weight) for defining moderately polluted harbor sediments for this metal. However, these concentrations are lower than the mean barium concentration of 482.1 µg/g in sediments collected from Lake Pontchartrain near New Orleans, Louisiana (USGS 2002c). The barium content in total suspended solids collected from the Mississippi River before it enters Lake Pontchartrain was 599 µg/g.

Barium concentrations in sediments near offshore drilling platforms are typically higher than unaffected sediments. Surficial and suspended sediments collected within 500 m of a drilling platform in the Santa Maria Basin offshore of central California contained barium at concentrations of 923 and 736 mg/kg dry

Table 6-3. Concentrations of Barium in Surface Soils of the United States[a,b]

Soil	Concentration[c]	
	Mean	Range
Sandy and lithosols on sandstone	400	20–1,500
Light loamy soils	555	70–1,000
Loess and soils on silt deposits	675	200–1,500
Clay and clay loamy soils	535	150–1,500
Alluvial soils	660	200–1,500
Soils over granite and gneisses	785	300–1,500
Soils over volcanic rocks	770	500–1,500
Soils over limestones and calcareous rocks	520	150–1,500
Soils on glacial till and drift	765	300–1,500
Light desert soils	835	300–2,000
Silty prairie soils	765	200–1,500
Chernozems and dark prairie soils	595	100–1,000
Organic light soils	265	10–700
Forest soils	505	150–2,000
Various soils	560	70–3,000
Mean concentration in Earth's crust[d]	500	—
Mean concentration in Earth's crust[e]	425	—

[a]Data obtained from Kabata-Pendias and Pendias (1984) unless indicated otherwise
[b]Data are for whole soil profiles
[c]Concentrations expressed as ppm dry weight
[d]Zenz et al. 1994
[e]Lide 2000

Source: Adapted from EPA 1995a

weight, respectively (Phillips et al. 1998). These values were higher (although not statistically significant) than the values of 869 and 687 mg/kg dry weight measured in surficial and suspended sediments, respectively, collected at a distance of 1,000 meters from the platform and are similar to the predrilling concentrations of barium in these sediments. In other California coastal sediments, for example the Southern California Bight, barium concentrations range from 145 to 1,259 ppm with an average of 720 ppm (Chow et al. 1978). Median barium concentration ranges in sediments from the lake system in Chiapas, Mexico were 54.4–121.2 and 50.3–155.3 µg/g dry weight in three lakes during the dry (June 2002) and rainy (September 2000) seasons, respectively (Pascual-Barrera et al. 2004). This lake system is an area of petroleum extraction and processing. Barium concentrations ranging from 180 to 2,800 µg/g dry weight (mean 729 µg/g dry weight) were reported in surface sediments (<63 µm fraction) collected in April 2002 from eight stations in Izmit Bay, Turkey (Pekey 2006).

Barium has been detected in soil and sediment samples collected at 369 and 260 of the 798 hazardous waste sites, respectively, where barium has been detected in some environmental medium (HazDat 2006). The HazDat information includes data from both NPL and other Superfund sites. Maximum concentrations of barium in soil (topsoil, <3 inches depth) ranged from 1.59 to 13,000 ppm in 84 onsite samples (HazDat 2006). In comparison, maximum concentrations of barium in soil (topsoil, <3 inches depth) ranged from 3 to 54,700 ppm in 28 offsite samples (HazDat 2006). Maximum concentrations of barium in sediment (lakes, streams, ponds, etc.) ranged from 13.1 to 17,600 ppm in 36 onsite samples (HazDat 2006). In comparison, maximum concentrations of barium in sediment (lakes, streams, ponds, etc.) ranged from 0.156 to 26,400 ppm in 92 offsite samples (HazDat 2006).

6.4.4 Other Environmental Media

Barium occurs in many foods at generally low levels (Table 6-4). In the Canadian Total Diet Study, the concentrations of barium were found to be less than 4 ppm (4,000 ng/g) in a variety of foods (Health Canada 2005). However, Brazil nuts have notably high concentrations of barium (3,000–4,000 ppm) (Beliles 1979). Some plants bioconcentrate barium from the soil (Beliles 1979; Reeves 1979; Schroeder 1970). The barium content in corn samples from Georgia, Missouri, and Wisconsin collected during a number of field studies ranged from 5 to 150 ppm with mean concentrations ranging from 15 to 54 ppm (Connor and Shacklette 1975). The barium content in other cultivated plants (e.g., lima beans, cabbage, soybeans, and tomatoes) from Georgia, Missouri, and Wisconsin ranged from 7 to 1,500 ppm with mean concentrations in various plants ranging between 38 and 450 ppm. The highest levels occurred in

Table 6-4. Concentrations of Barium in Food Obtained from the Canadian Total Diet Study Between 1993 and 1999

Food Categories	Concentration (ng/g)	
	Average[a]	Range[b]
Milk	71.22	67.96–73.24
Dairy produce (ice cream, yogurt, cheese, cream)	332.37	70.61–962.93[c]
Meats (beef, pork veal, lamb, organ meats)	131.82	12.06–237.57
Eggs	456.69	456.69
Poultry (chicken, turkey)	52.53	52.53
Fish (marine, fresh water, canned) and shellfish	137.28	36.17–481.34
Soups (meat, cream, tomato, dehydrated)	130.01	119.66–154.53
Breads, cereals, pasta, rice, pastries (cake, pies)	891.16	45.86–3,840.40[d]
Vegetables	425.69	47.99–2,282.23[e]
Fruits	570.33	57.62–3,750.03[f]
Oils, fats, butter	32.45	20.67–53.08
Candy, syrups, jams, gelatin, puddings, honey, sugar	300.60	4.86–903.07[g]
Peanut butter and peanuts	2,919.11	2,919.11
Beverages (beer, wine, coffee, tea, soft drinks, tap water)	70.94	13.05–151.82
Baby foods and formula	196.46	46.98–481.85
Frozen entrees	457.76	393.57–594.11
Processed foods (pizza, burgers, French fries, hot dog, etc.)	516.96	278.43–864.58

[a]Values represent the average barium concentration in the foods covered under the individual food categories.
[b]Values represent the range of average concentrations of the food items covered under the individual food categories.
[c]The highest barium concentrations were found in unprocessed cheeses (962.93 ng/g).
[d]The highest barium concentrations were found in wheat and bran cereals (3,840.40 ng/g), whole wheat bread (1,494.06 ng/g), muffins (1,434.30 ng/g), and cookies (1,029.13 ng/g).
[e]The highest barium concentrations were found in beets (2,282.23 ng/g) and carrots (1,309.25 ng/g).
[f]The highest barium concentrations were found in raspberries (3,750.03 ng/g) and strawberries (1,176.48 ng/g).
[g]The highest barium concentrations were found in chocolate candy bars (903.07 ng/g).

Source: Health Canada (2005)

cabbage from Georgia and soybeans from Missouri and the lowest levels occurring in Georgia tomatoes (Connor and Shacklette 1975).

Grippo et al. (2006) measured various metal concentrations in dietary supplements purchased from random local vendors in the Little Rock, Arkansas area between 2002 and 2003. Barium concentrations in botanicals were 0.0200 and 15.4 ng/g in samples of milk thistle and kava kava, respectively. Barium concentrations in ephedra-containing supplements were 0.0400 and 93.3 ng/g in Virgin Earth and Xenadrine RFA-1, respectively. The authors noted that all metals measured in this study were detected at concentrations below toxic levels or physiological limits for daily intake, where such limits have been identified (Grippo et al. 2006).

The Wyoming Game and Fish Department collected game fish during the 2000–2001 season to survey the state's fisheries for metal contamination. Ninety-six fish composites (fillets) were collected, representing 11 species, from 28 lakes and reservoirs across Wyoming. In this study, barium concentrations were at or below the method detection limit of 0.05 mg/kg (Dailey et al. 2005). Mean barium concentrations ranging from 0.057 to 0.255 mg/kg wet weight were reported in muscle tissue of five species of sturgeons collected from the Caspian Sea (Pourang et al. 2005).

Barium is also found in anaerobic sewage sludge at concentrations ranging from 100 to 9,000 ppm (mean concentration of 800 ppm) and in aerobic sewage sludge at concentrations ranging from 100 to 300 ppm (mean concentration of 200 ppm) (Sommers 1977).

Barium concentrations in leachates from municipal landfills range from 0.11 to 9,220 μg/L (EPA 1990, 1991; Roy 1994).

Barium concentrations in fertilizers and soil amendments range from <0.2 to 669 μg/g mean (Raven and Loeppert 1997). The highest levels are in tilemsi phosphate rock (669 μg/g), austenite (408 μg/g), milorganite (165 μg/g), manure (153 μg/g), and compost (131 μg/g). There is some concern that continued use of fertilizers and soil amendments, which contain high amounts of barium and other metals, may result in an accumulation of barium in agricultural soils. The accumulation of barium in soils that is due to the continued use of fertilizers and soil amendments and the potential for increased content of barium in agricultural products and potential harm to the environment have not yet been assessed (Raven and Loeppert 1997).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The primary routes of exposure of humans to barium are consumption of food and water and inhalation of ambient air (ICRP 1974; Reeves 1979; WHO 2001). Based on compliance monitoring data from the Federal Reporting Data System (FRDS), of the approximately 214 million people in the United States who are connected to a public water supply, it is estimated that about 150,000 people are exposed to barium concentrations greater than EPA's MCL of 2.0 mg/L (2,000 µg/L) (EPA 2002a). However, since 94% of all samples collected from public water supplies of the 100 largest cities in the United States had barium concentrations <100 µg/L (Durfor and Becker 1964), it is likely that most of the people connected to a public water supply receive drinking water with barium concentrations below the MCL. In a survey of drinking water from residences in EPA Region V (Indiana, Illinois, Michigan, Minnesota, Ohio, and Wisconsin) taken from the National Human Exposure Assessment Survey (NHEXAS) in 1995, an average barium concentration of 30 µg/L was obtained, with a 90th percentile value of 77 µg/L (Thomas et al. 1999). Assuming an average adult drinking water consumption rate of 2 L/day and that barium is present at concentrations of 30 µg/L, the average adult daily intake of barium through the consumption of drinking water would be 60 µg/day (0.86 µg/kg/day for a 70-kg adult). However, the International Commission for Radiation Protection (ICRP) estimates that the gastrointestinal absorption of barium is <5% (ICRP 1973).

The International Commission on Radiological Protection (ICRP 1974) has estimated that intake of barium through inhalation ranges from 0.09 to 26 µg/day. Based on reported urban air concentrations for barium (<0.005–1.5 µg/m^3) (Tabor and Warren 1958) and assuming an average adult ventilation rate of 20 m^3/day (EPA 1989), the calculated daily respiratory intake of barium ranges from <0.1 to 30 µg, which is comparable to the ICRP estimated intake range above. Based on the 8-hour time-weighted average threshold limit value (TLV) in workplace air of 500 µg/m^3 (ACGIH 2004), and assuming an 8-hour inhalation of 10 m^3 of air, a daily barium workplace intake of 5,000 µg can be calculated. NAS (1977) estimated that 75% of inhaled barium could be absorbed into the bloodstream if soluble barium salts were involved.

Since average ground level concentrations of an emission vary with the distance from the emission point, the population around a source site will be exposed to differing emission levels. Using an average population density of 27 persons/km^2 (based on actual population data from areas surrounding barium production and processing plants), it has been estimated that approximately 0–886 persons within an area of up to 32.8 km^2 around a source site could be exposed to soluble barium compound concentrations of

>1.67 μg/m^3 in ambient air (Reznik and Toy 1978). Assuming that the average adult daily ventilation rate is 20 m^3 (EPA 1989), breathing these ambient air barium concentrations would result in daily respiratory intakes of >32 μg. No other correlations have been established between barium concentrations in air and geographical areas or land-use types.

The day-to-day intake of barium is likely to vary with the quantity and types of food ingested since the barium content in foods varies widely (Schroeder 1970). Based on consumption of food and beverages in long-term balance studies of four individuals, daily barium intake was estimated to range from 650 to 1,770 μg/day, or from 9.30 to 25.3 μg/kg body weight/day based on an adult weight of 70 kg (Tipton et al. 1966, 1969). Assuming an estimated average barium intake of 60 μg/day from drinking water that is based on the barium concentrations in drinking water obtained in the NHEXAS EPA Region V study (Thomas et al. 1999) and a consumption of 2 L of water per day, the barium intake from the consumption of non-drinking water dietary sources alone would range from 590 to 1,710 μg/day. Thus, food is typically the primary source of barium exposure for the general population. Gastrointestinal absorption of barium from food was reported to be approximately 6% (ranging from 1 to 15%) (ICRP 1974). However, reevaluation of this ICRP data and the data from other studies (Harrison et al. 1956; LeRoy et al. 1966); Tipton et al. 1969, Schroeder et al. 1972) using the methods of re-estimating barium absorption, which are based on current information of systemic kinetics of barium (Leggett 1992), suggest that gastrointestinal absorption of barium may be higher, generally ranging between 7 and 30% and could be as high as 95% in some individuals.

In the Canadian Total Diet Study (TDS) of 1993–1999, the average barium intake in individuals surveyed was found to be highest in young children (Health Canada 2005). The average barium intake ranged from 20.760 to 25.251 μg/kg body weight/day for children ages 0–4 years old (Table 6-5). For individuals older than 4 years, the average barium intake decreased for both males and females with increasing age to values of 9.704 (20–39 years) and 7.839 (>65 years) μg/kg body weight/day in males and 8.418 (20–39 years) and 7.546 (>65 years) μg/kg body weight) in females. The average daily barium intakes from the Canadian TDS for males and females of all ages (8.817 μg/kg body weight/day) is in reasonable agreement with the low end of the daily intake range for barium of 9.30 μg/kg body weight/day determined by Tipton et al. (1966, 1969).

Mean daily balances (excluding loss via hair and sweat) determined from long-term balance studies of four adult subjects ranged from a negative balance of 800 μg to a positive balance of 890 μg (Tipton et al. 1966, 1969). Based on data from these studies, Schroeder (1970) estimated that human daily intake

Table 6-5. Average Dietary Intake of Barium in Different Age/Sex Groups from the Canadian Total Diet Study (1993–1999)

Sex	Age	Intake[a]
Male and female	0–1 months	20.760
Male and female	2–3 months	23.350
Male and female	4–6 months	21.414
Male and female	7–9 months	21.213
Male and female	10–12 months	22.823
Male and female	1–4 years	25.251
Male and female	5–11 years	18.741
Male	12–19 years	11.759
Male	20–39 years	9.704
Male	40–64 years	8.976
Male	≥65 years	7.839
Female	12–19 years	9.280
Female	20–39 years	8.418
Female	40–64 years	7.855
Female	≥65 years	7.546
Male and female	All ages	8.817

[a]micrograms barium per kilogram body weight per day

Source: Health Canada (2005)

from food (1,160 µg), water (80 µg), and air (10 µg) would be approximately 1,250 µg, and that loss from urine (180 µg), feces (1,010 µg) and other sources (e.g., sweat and hair) (85 µg) would be 1,275 µg. Using these latter estimates of barium intake and loss, a negative barium balance of 25 µg would occur. According to ICRP, the average daily intake of barium from food and fluids (750 µg) and ambient air (0.09–26 µg) ranges from 750 to 776 µg. In addition, ICRP (1974) estimated that approximately 825 µg of barium is lost daily through the urine (50 µg), feces (690 µg), sweat (10 µg), and hair (75 µg). These intake and loss estimates indicate a negative daily balance of up to 75 µg. However, these negative daily balance values of 25 and 75 µg are not significant. Also, it is not expected that a negative daily balance would maintain a total body content of barium for a 70-kg adult of 22,000 µg, a value that was estimated from a study of barium content in major human organs and tissues (ICRP 1974; Schroeder et al. 1972). Ninety-three percent of this barium was found in bone and connective tissue. The remaining 7% of barium exists largely in fat, skin, and lungs.

Barium content in the human population has been determined in urine and major organs and tissues in more current studies. Barium concentrations in urine for the United States population aged 6 years and older were measured in the Third National Health and Nutrition Examination Survey (NHANES). The geometric mean (95% confidence interval) for the creatinine-adjusted levels of barium in urines for all ages was 1.44 (1.31–1.58) µg per gram of creatinine (CDC 2005). Within age groups, the geometric means for the barium concentration in urine decreased as a function of age, from 2.20 µg per gram of creatinine (6–11 years) to 1.45 µg per gram of creatinine (12–19 years) and 1.37 µg per gram of creatinine (20 years and older). The geometric mean concentration of barium in females (1.59 µg per gram of creatinine) was slightly higher than in males (1.30 µg per gram of creatinine). As a function of ethnicity, non-Hispanic whites had the highest geometric mean barium concentrations (1.62 µg per gram of creatinine) followed by Mexican Americans (1.18 µg per gram of creatinine) and non-Hispanic African Americans (0.891 µg per gram of creatinine). A median urinary concentration of 1,146 ng/L (range 295–5,250 ng/L) was reported in urine of 50 healthy individuals, aged 20–68 years, in central Italy (Alimonti et al. 2005).

Occupational exposure to barium primarily occurs in workers and miners who inhale barium sulfate (or the ore, barite) and barium carbonate dust during the mining of barite and the manufacturing and processing (e.g., mixing, grinding, and loading) of barium compounds (Beliles 1979; Reznik and Toy 1978; Schroeder 1970). Inhalation exposure to barium is also known to occur for industrial welders, especially those using barium-containing stick electrodes and self-shielded flux core wires, and those

working in ceramic factories (Ramakrishna et al. 1996; Roig-Navarro et al. 1997; WHO 2001; Zschiesche et al. 1992).

Data from a workplace survey, the National Occupational Exposure Survey (NOES), conducted by NIOSH from 1980 to 1983, estimated the number of workers potentially exposed to various chemicals in the workplace in 1980 (NIOSH 1989a), including a separate tally of female workers. The data for barium and barium compounds included in the survey are summarized in Table 6-6. The NOES database does not contain information on the frequency, concentration, or duration of exposure of workers to any of the chemicals listed therein. This is a survey that provides only estimates of the number of workers potentially exposed to chemicals in the workplace.

6.6 EXPOSURES OF CHILDREN

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

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

The main exposures of children to barium are expected to occur mainly from the diet or by dermal contact with barium-containing dust, with minor exposures through barium in air. Data on the daily intake of barium in the total diet of children in the United States were not located in the available literature. However, the average daily intake of barium in children has been determined in a Canadian Total Diet Study (1993–1999), showing that children ages 0–48 months have the highest barium intake through their diet in comparison to older children (>4 years) and adults (Health Canada 2005). The average barium intake in young male and female children increased from 20.760 for infants (0–1 month) to 25.251 μg/kg body weight/day for children ages 1–4 years (Table 6-5). For older children (>4 years), there is a continual decrease in the average daily barium intake, with values of 18.741 μg/kg body weight/day for

Table 6-6. Number of Workers Potentially Exposed to Barium and Barium Compounds

Chemical	Number of plants	Total workers (female workers)
Barium	815	10,308 (3,598)
Barium carbonate	4,494	61,019 (6,889)
Barium chloride	4,293	57,767 (15,249)
Barium hydroxide	1,423	35,351 (12,208)
Barium oxide (BaO_2)	46	511 (325)
Barium nitrate	353	9,625 (2,699)
Barium sulfate	20,089	305,887 (83,800)
Barium sulfide	7	7 (0)
Chromic acid (H_2CrO_4), barium salt (1:1)	20	3,546 (1,984)

Source: NIOSH 1989a

individuals aged 5–11 years and then down to 11.759 µg/kg body weight/day for males and 9.280 µg/kg body weight/day for females aged 12–19 years. It is expected that the data obtained from the Canadian Total Diet Study will reasonably approximate the daily barium intake for children living in the United States. It is estimated that for children in the United States, the barium intake through drinking water will range between 36 and 60 µg/day. This estimate is based on an average concentration of 30 µg barium/L in drinking water within the United States (Thomas et al. 1999) and the consumption of 1.2–2.0 L water/day. A factor to be taken into account is that fractional intestinal absorption of metals in young children, as in young mammals, may be higher than in adults (Foulkes and Bergman 1993). Dermal contact with barium in household dust is not expected to result in uptake of barium through the skin. Oral intake of barium through hand-to-mouth exposures to barium-containing dust is likely to occur. However, it is not known how much barium is taken in through this route of exposure. There is also the potential of oral intake of barium through the licking or ingestion of crayons or water colors, but it is not known how much barium is ingested or how much is bioavailable (Rastogi and Pritzl 1996).

Dietary intake of barium in 3-month-old infants has been given by Biego et al. (1998) for exclusive consumption of various types of milk. The average barium intake from the consumption of breast milk only was determined to be 4 µg/day. Barium intake increases with exclusive consumption of bottled milk (39 µg/day), evaporated milk (42 µg/day), formula (44 µg/day), and dried milk (59 µg/day). The highest average intake of barium occurred with exclusive consumption of soya milk (91 µg/day). These intakes are based on an average daily intake of milk of 700 mL.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

The general population is commonly exposed to barium primarily through ingestion of drinking water and consumption of food and beverages. However, certain populations face greater than average exposures to this element due to environmental sources, such as drinking water (EPA 1987). High levels of barium have been reported in groundwater from deep rock and drift wells in several communities in northeastern Illinois (Brenniman et al. 1981; Calabrese 1977) where barium is a naturally occurring geochemical pollutant found almost exclusively in the Cambrian-Ordovician Aquifer (Gilkeson et al. 1978). Other populations that might receive increased exposure to barium are consumers of crops grown on soils that have been used for the land farming of waste oil-well drilling muds (Bates 1988). Individuals who work at or live near barium mining, manufacturing, or processing plants might inhale higher ambient air concentrations or increased amounts of fugitive dust containing barium particulates. Populations living in the vicinity of the NPL sites known to be contaminated with barium may also be exposed to higher than

background levels of the compound through contact with contaminated waste site media or barium in offsite air or water. Barium has been measured in air, surface water, and groundwater collected offsite of some NPL sites (HazDat 2006). No information was found regarding the sizes of these populations or their intake levels of barium.

6.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of barium is available. Where adequate information is not available, ATSDR, in conjunction with 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 barium.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of metallic barium and its inorganic compounds have been well characterized (Boffito 2002; CHRIS Manual 2005; Dibello et al. 2003; DOT 2004; Genter 2001; HSDB 2007; Kresse et al. 2007; Lewis 1997; Lide 2005; NIOSH/OSHA 1978; NIOSH 1999; Budavari et al. 2001; OHM/TADS 1989; Parmeggiani 1983; Perry and Chilton 1973; RTECS 2007; Lewis 2000; Stokinger 1981; Weast 1989). Physical and chemical properties of organic compounds of barium have not been comprehensively examined probably due to the limited extent of formation of these compounds. However, further study of the properties of these compounds would help in understanding their role in the environmental fate and transport of barium, particularly at hazardous waste sites where high levels of organic contaminants might be present.

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The TRI, which contains this

information for 2004, became available in May of 2006. This database is updated yearly and should provide a list of industrial production facilities and emissions.

Because barium compounds occur naturally and are widely used in oil well drilling muds, in steel, rubber and plastic products, glass and ceramics, chemical, and pyrotechnics industries, in insecticides, and as a smoke suppressant in diesel fuels (Bodek et al. 1988; Dibello et al. 2003; ILO 1983; Kirkpatrick 1985; Meister 2004; Stokinger 1981; Venugopal and Luckey 1978; WHO 2001; Worthing 1987), the potential for human exposure to these compounds, such as through ingestion of food and water or inhalation of ambient air, is substantial. Recent data on production volumes and import and export of barite and some barium compounds (e.g., barium chloride, barium carbonate, barium hydroxide, and barium oxide) are available (USGS 2006). In addition, only limited information on disposal of barium compounds was available (HSDB 2007; IPCS 1991; NIOSH/OSHA 1978). Additional information on production, import, export, and disposal would be useful in assessing the potential for the release of, and exposure to, barium compounds.

Environmental Fate. The partitioning of barium in environmental media is influenced by the specific form of the compound and such site-specific conditions as pH and cation exchange capacity (Bates 1988; Bodek et al. 1988; Bowen 1966; Giusti et al. 1993; Kabata-Pendias and Pendias 1984; Lagas et al. 1984; Tanizaki et al. 1992). Upon release to the environment, barium is most likely to partition to soils and sediments (Chow et al. 1978; DOE 1984; Rai et al. 1984; WHO 2001). Barium is transported in the atmosphere, surface waters, soil runoff, and groundwater. In surface waters and soils, barium may ionize and form various salts depending on the pH and the availability of anions (Bates 1988; Bodek et al. 1988; Bowen 1966; Kabata-Pendias and Pendias 1984; Lagas et al. 1984; WHO 2001). Additional information on the transport and transformation of barium in the atmosphere would be useful in developing a more complete understanding of the environmental fate of barium compounds.

Bioavailability from Environmental Media. Barium is absorbed following ingestion (Chou and Chin 1943; Cuddihy and Griffith 1972; McCauley and Washington 1983; Taylor et al. 1962) and inhalation (Cuddihy and Ozog 1973b). The bioavailability of barium from air, water, and food has been examined rather extensively in animals (Chou and Chin 1943; Cuddihy and Griffith 1972; McCauley and Washington 1983; Taylor et al. 1962) and humans (Tipton et al. 1969). However, bioavailability from soil has not been studied. Since soil is an important repository for barium, information on barium absorption from ingested soil would be useful in developing an understanding of the potential for exposure following ingestion of contaminated soils, particularly at hazardous waste sites.

Food Chain Bioaccumulation. There is information that barium bioconcentrates in certain plants and aquatic organisms (Aruguete et al. 1998; Bowen 1966; Hope et al. 1996; IPCS 1991; Schroeder 1970; WHO 2001). However, the extent to which plants bioconcentrate barium from soil or to which uptake occurs in terrestrial animals is not well characterized. Further studies on the bioconcentration of barium by plants and terrestrial animals and on the biomagnification of barium in terrestrial and aquatic food chains would be useful to better characterize the environmental fate of barium and define the importance of food chain accumulation as a source of human exposure.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of barium in contaminated media at hazardous waste sites are needed so that the information obtained on levels of barium in the environment can be used in combination with the known body burden of barium to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites. The need for additional information on the relationship between barium exposure and levels of barium achieved *in vivo* is essential if such concentrations are to be used as biomonitors of exposure.

Barium has been detected in the atmosphere (Bowen 1979; EPA 1984; Hildemann et al. 1991; IPCS 1991; Schauer et al. 1999; Shahin et al. 2000; WHO 2001; Winkler 2002), surface water (Barnett et al. 1969; Bowen 1979; DOI 1970; Durfor and Becker 1964; Durum and Haffty 1961; Elinder and Zenz 1994; EPA 2005c; Kopp 1969; Longerich et al. 1991; McCabe et al. 1970; Neal et al. 1996; Saleh and Wilson 1999; Tuovinen et al. 1980), groundwater (Bruce and McMahon 1996; Calabrese 1977; Hudak and Wachal 2001; Kojola et al. 1978), soils (Bowen 1979; Bradley et al. 1994; EPA 1995a; Kabata-Pendias and Pendias 1984; Lide 2005; Schroeder 1970; Shacklette and Boerngen 1984; Zenz et al. 1994), and foodstuffs (Beliles 1979; Connor and Shacklette 1975; Health Canada 2005; Schroeder 1970). There are reliable data to characterize the potential for human exposure via intake of drinking water (Durfor and Becker 1964; Hadjimarkos 1967; Thomas et al. 1999), and foods (Health Canada 2005; Tipton et al. 1966, 1969). Recent data on barium levels in plants and ambient air, soils, and groundwater, particularly from hazardous waste sites, would be useful in helping to develop a more complete understanding of the potential for human exposure.

Exposure Levels in Humans. Barium can be detected in blood, urine, feces, and biological tissues (CDC 2001, 2003; Mauras and Allain 1979; Schramel 1988; Shiraishi et al. 1987). However, there are no data correlating barium levels in tissues and fluids with exposure levels. Recent biomonitoring data exist for the U.S. general population (CDC 2005), although there are limited monitoring data for occupational

exposure and for populations living near hazardous waste sites. This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Child health data needs relating to susceptibility are discussed in Section 3.12.2, Identification of Data Needs: Children's Susceptibility.

Data on the exposure of children in the United States to barium are very limited. It is expected that the largest exposure to barium will be through the diet. Therefore, market basket surveys or total diet studies similar to those conducted by the U.S. Food and Drug Administration would be useful for providing data on typical levels of exposure via dietary intake for children in the United States. Data are available for barium intake in Canadian children obtained from a 1993–1999 total diet study (Health Canada 2005) and in a separate study (Biego et al. 1998) in infants (3 months old) from the exclusive consumption of breast milk and other types of milk.

Exposure Registries. No exposure registries for barium were located. This substance is not currently one of the compounds for which a sub-registry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for sub-registries 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.

6.8.2 Ongoing Studies

Three ongoing studies concerning the fate/transport of barium and measurement of barium in environmental media were identified in the Federal Research in Progress database (FEDRIP 2005). These studies are summarized in Table 6-7. No other pertinent ongoing studies were identified.

Table 6-7. Ongoing Studies on Environmental Fate and the Potential for Human Exposure to Barium and Barium Compounds

Investigator	Affiliation	Research description	Sponsor
Batiza, R	Oregon State University	The proposed research will attempt to quantify the cold seep barite contribution to the marine sediment record by first quantifying the cold seep barite (an important carrier of barium) contribution to barium and radon fluxes within the San Clemente basin and then, secondly, quantify the effects of this source on the chemical signature of barite in the basin sediments.	NSF
Naehr, TM; MacDonald, IR	Texas A&M University Corpus Christi	Acquisition of a basic powder x-ray difractometer system for qualitative and quantitative phase analysis in studies of (1) geologic materials to enhance research into the formation of diagenetic barite and silicate minerals in sediments from the Peruvian Continental Margin, (2) the authigenic seafloor deposits at sites of active submarine fluid expulsion in the Gulf of Mexico region to elucidate the geo-chemical environment at these sites, and (3) barium and other metals in soil and sediment samples.	NSF
Odom, JW	Auburn University	Develop analytical techniques for total and plant-available forms of barium and other metals in soils and for total analysis of these metals in plant material; determine the normal occurrence of both total and extractable forms of these elements in selected soil profiles; and ascertain the availability of soil test calibration data and soil test procedures for these elements.	Hatch

NSF = National Science Foundation

Source: FEDRIP 2005

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7. ANALYTICAL METHODS

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

7.1 BIOLOGICAL MATERIALS

Inductively coupled plasma-atomic emission spectrometry (ICP-AES) has been used for measuring low levels of barium in the blood, urine, and bones of humans and animals (Mauras and Allain 1979; Schramel 1988; Shiraishi et al. 1987) (see Table 7-1). In general, biological samples are nebulized and the resulting aerosol is transported to the plasma torch. Atomic-line emission spectra are produced by the inductively coupled plasma for specific element and the intensities of the lines (bands) are monitored by a photomultiplier tube. A line emission at 455.50 nm was observed for barium (Mauras and Allain 1979; Oppenheimer et al. 1984). Detection limits of 0.25 μg barium/L of urine, 0.6 μg barium/L of blood, and 0.0005 μg of barium per gram of bone were achieved (Mauras and Allain 1979; Shiraishi et al. 1987). Advantages of ICP-AES technique include moderate costs, fairly rapid analysis time, and high sensitivity (Mauras and Allain 1979; Oppenheimer et al. 1984). The presence of spectral interferences is a disadvantage of ICP-AES technique. These interferences are caused when a sample contains elements or compounds that have analytical emission lines (bands) that overlap the line chosen for the analyte. Boric acid or sodium borate (at a concentration of >100 mg boron/L of sample) was reported to interfere with the line emission spectra of barium at 455.50 nm (Mauras and Allain 1979).

Neutron activation analysis (NAA) technique has also been used for determining low levels of barium in human blood (Olehy et al. 1966). This technique is based on the interaction of the nuclei of individual barium atoms with neutron irradiation, resulting in the emission of x-rays (photons). Detection limits of 7 μg barium/L of erythrocyte and 66 μg barium/L of plasma were obtained (Olehy et al. 1966). The advantages of the NAA technique include minimal sample preparation and the fact that destruction of the

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urine and blood	Dilute sample with demineralized water, introduce into the plasma and analyze	ICP-AES	0.25 µg/L (urine); 0.6 µg/L (blood)	3–7% coefficient of variation	Mauras and Allain 1979
Urine	Dilute sample with demineralized water, introduce into the plasma and analyze	ICP-AES	0.2 µg/L	No data	Schramel 1988
Erythrocyte and plasma	Ash sample, digest with acid and irradiate	NAA	7 µg/L (erythrocyte); 66 µg/L (plasma)	28.5% RSD (erythrocyte) 7.6% RSD (plasma)	Olehy et al. 1966
Biological tissues	Digest sample in acid; precipitate as the sulfate and analyze	Gravimetry	No data	No data	Borchardt et al. 1961
Visceral materials (intestine, stomach, liver, spleen, and kidney)	Ash sample and analyze	AES	No data	86.8–130.5%	Baisane et al. 1979
Fetus bones	Ash sample and digest with acid	ICP-AES	0.0005 µg/g	0.5% RSD	Shiraishi et al. 1987

AES = atomic emission spectroscopy; ICP-AES = inductively coupled plasma-atomic emission spectrometry; NAA = neutron activation analysis; RSD = relative standard deviation

sample is not needed to conduct the analysis. Disadvantages of this technique include its high costs and a nuclear reactor may not be readily available to many laboratories.

Gravimetric and spectrometric techniques have also been described for quantifying barium in tissues. Borchardt et al. (1961) measured barium in tissues gravimetrically following digestion of 15–20 grams of sample in a 2:1 (by volume) mixture of sulfuric and nitric acids. The barium in the samples was precipitated out as the sulfate, dried, and weighed. No limits of detection were given. Recovery of barium from acid-digested tissues can be impaired when organic ions react with barium and interfere with the formation of the barium sulfate precipitate. However, Borchardt et al. (1961) reported that no such interferences were observed in their assay and that complete recovery of barium from the sample was obtained. In another method, Baisane et al. (1979) used atomic emission spectroscopy to measure barium in visceral material. The method required ashing of tissue samples by heating with a burner or a muffle furnace and then fusing the ash with graphite and lithium carbonate. The barium in the fused ash was quantified by using an electric arc as an excitation source and monitoring the barium emission at 2,335 Å. Limits of detection were not given, but recoveries ranged from 86.8 to 130.5%.

7.2 ENVIRONMENTAL SAMPLES

Atomic absorption spectroscopy (AAS) is the most prevalent analytical technique for measuring low levels of barium in air, water, waste water, geological materials (calcium carbonate), unused lubricating oil, and diagnostic meals containing barium sulfate (see Table 7-2).

Samples may be prepared for AAS in a variety of ways (EPA 1974, 1994a, 1994b, 1996; Hui-Ming and Yao-Han 1984; Johnson et al. 1983; Murata and Noguchi 1974; Pierce and Brown 1977; Renshaw 1973; Sharp and Knevel 1971; Sugiyama et al. 1984). Acid digestion with nitric acid is the most common method of preparation. Sample dilution with nitric acid or other agents to solubilize barium from the matrix can also be employed. If the concentration of barium in the dissolved sample is very low, preconcentration techniques such as chelation or extraction may be employed.

Flame atomic absorption spectroscopy (FAAS) (Methods 208.1 and 7080) and graphite furnace atomic absorption spectroscopy (GFAAS) (Methods 208.2 and 7081) are the techniques recommended by the Office of Solid Waste and Emergency Response of EPA for determining ppb (µg/L) levels of barium in water and waste water (EPA 1974, 1979, 1992, 1994a, 1994b). Parts-per-trillion (sub µg/L) levels of barium in seawater and freshwater have been detected by GFAAS (Epstein and Zander 1979; Roe and Froelich

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Collect sample on cellulose membrane and extract with hot acid; evaporate extract to dryness and dissolve residue in acid	FAAS	2 µg per sample	102%	NIOSH 1994 (Method 7056)
Air	Collect sample on cellulose or PVC membrane; extract with hot acid and evaporate at 150 °C to near dryness; dissolve residue in acid	ICP-AES	0.005 µg per sample	97.7–102.4%	NIOSH 2003 (Method 7300)
Water	Reflux with addition of HNO_3 and HCl; filter	ICP-MS	0.8 µg/L	95%	EPA 1994a (Method 200.8)
	Reflux with addition of HNO_3 and HCl; filter	ICP-AES	1 µg/L	92%	EPA 1994b (Method 200.7)
	Acidify with HNO_3; filter	FAAS	100 µg/L	94%	EPA 1974 (Method 208.1)
	Reflux with addition of HNO_3 and HCl	FAAS	33.5–132 µg/L (working range)	104.5–106.9% (33.5 µg/L)	ASTM 2000 (Method D4382)
	Acidify sample and pass through ion-exchange resin	FAAS	3 µg/L	11.6% RSD	Pierce and Brown 1977
	Pass sample through ion-exchange resin	FAES	µg/L levels	No data	Johnson et al. 1983
	Extract sample with buffered HFA solution	FAAS	5 µg/L	No data	Edelbeck and West 1970
	No data	GFAAS	7 µg/L	90–110%	Fagioli et al. 1988
	Inject sample directly into graphite furnace	GFAAS	0.6 µg/L (seawater); 0.2 µg/L (freshwater)	13% RSD	Roe and Froelich 1984
Seawater and brackish water	Acidify and inject	DCAP-AES	10–20 mg/L (working range)	108.8% (10 mg/L)	ASTM 1999 (Method D3986)
Water and waste water	Digest sample and evaporate to dryness; dissolve residue in acid	FAAS, GFAAS	100 µg/L (FAAS); 2 µg/L (GFAAS)	94–113% (FAAS); 96–102% (GFAAS)	EPA 1974, 1979, 1992, 1994 (Methods 208.1, 208.2, 7080, and 7081)
Industrial waste water	Digest sample; mix with cation-exchange resin; dry and analyze	XFS	290 µg/L (in 500 mL samples)	5.1% RSD	Murata and Noguchi 1974

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Unused lubricating oil	Dissolve sample in 2-methyl-propan-2-ol:toluene (3:2); add potassium naphthenate solution	FAAS	No data	No data	Holding and Rowson 1975
Rocks and minerals (calcium carbonate)	Precipitate barium from sample; dissolve in ammoniacal solution of EDTA	FAAS	Low µg/g levels	118%	Bano 1973
Soil	Digest sample in HNO_3 and H_2O_2, filter, dilute with acid	GFAAS	0.2 µg/g dry weight	96%	EPA 1978, 1996 (Methods 3050B and 208.2)
Sediment, soil, rocks	Digest sample in a mixture of HCl, HNO_3, and $HClO_4$ by heating to dryness; resuspend residue in HNO_3 and H_2O_2 and heat; cool and dilute in 1% HNO_3	ICP-MS	0.15 ppm	96–102%	USGS 2002a (Method T20)
Sediment, rocks, plants	Digest sample in a mixture of HF, HNO_3, and $HClO_4$ by heating to dryness; resuspend residue in $HClO_4$ and heat to dryness; resuspend in aqua regia, dilute with 1% HNO_3, and reheat	ICP-AES	0.3 ppm	95–106%	USGS 2002b (Methods E011 and T01)
Food, beverage	Homogenize sample; microwave digestion of sample in HNO_3; centrifuge	ICP-AES	0.03 mg/kg (food) 0.004 mg/kg (beverage)	86–94% (food) 86–92% (beverage)	EPA 1995b
Diagnostic meals containing barium sulfate	Add sample to EDTA solution and warm	FAAS	No data	98.6–102.5%	Sharp and Knevel 1971
Compound formulation ($Ba^{14}CO^3$)	Prepare solution of sample in EDTA and count	Scintillation spectrometry	No data	No data	Larsen 1973

$Ba^{14}CO_3$ = radiolabeled barium carbonate; DCAP-AES = direct-current argon plasma-atomic emission spectroscopy; EDTA = ethylenediamine tetraacetic acid; FAAS = flame atomic absorption spectroscopy; FAES = flame atomic emission spectroscopy; GFAAS = graphite furnace atomic absorption spectroscopy; HCl = hydrochloric acid; $HClO_4$ = perchloric acid; HF = hydrofluoric acid; HFA = hexafluoroacetylacetone; HNO_3 = nitric acid; H_2O_2 = hydrogen peroxide; ICP-AES = inductively coupled plasma-atomic emission spectroscopy; ICP-MS = inductively coupled plasma-mass spectrometry; PVC = polyvinyl chloride; RSD = relative standard deviation; XFS = x-ray fluorescence spectroscopy

1984). The advantages that GFAAS and FAAS techniques offer are that they are sensitive techniques, use relatively simple and inexpensive instrumentation, and have high accuracy and precision. In addition, GFAAS technique requires a small amount of sample and is more sensitive than FAAS methodology for determining barium in aqueous media (Edelbeck and West 1970; Oppenheimer et al. 1984).

FAAS (Method 7056) is the technique recommended by NIOSH for detecting soluble barium compounds in air (NIOSH 1994). AAS has also been employed for detecting barium in air at 20 ppb (Miner 1969a).

Other analytical techniques that have been employed for measuring barium and its compounds in environmental media include x-ray fluorescence spectroscopy (XFS), neutron activation analysis (NAA), direct current argon plasma-atomic emission spectroscopy (DCAP-AES), inductively coupled plasma-mass spectrometry (ICP-MS), inductively coupled plasma-atomic emission spectroscopy (ICP-AES), scintillation spectroscopy, and spectrography (Boothe and James 1985; Landis and Coons 1954; Larsen 1973; Murata and Noguchi 1974; Oppenheimer et al. 1984). XFS and NAA methods are less sensitive than other available analytical methods for measuring barium in environmental media. Scintillation spectroscopy and spectrography are less commonly used to measure barium in the environment relative to other analytical methods. ICP-MS and ICP-AES offer low detection sensitivities that are typically at the ppb level and are becoming more routinely used for analysis of samples with complex mixtures of metals and metal complexes. For example, ICP-AES (Method 7300) is a technique recommended by NIOSH for analyzing soluble barium compounds in air with a limit of detection of 0.005 μg per sample (approximately 0.005 $\mu g/m^3$), which is 400 times less than the detection limit for another NIOSH method (7056) that uses FAAS as the technique to quantify barium in air (NIOSH 1994, 2003). ICP-AES (Methods E011 and T01) and ICP-MS (Method T20) are recommended by the U.S. Geological Survey (USGS) for measuring the barium content in sediments and rocks (USGS 2002a, 2002b). ICP-AES is also used to quantify barium and other trace metals in food and beverages with minimum detection limits of 0.004–0.3 mg/kg (ppm) and recoveries of 86–94% (EPA 1995b). ICP-MS is a useful technique for isotopic analysis of barium to determine sources of environmental emissions of barium compounds.

7.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of barium is available. Where adequate information is not available, ATSDR, in conjunction with 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 barium.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

Exposure. Several methods are available for measuring biomarkers of exposure. ICP-AES is the analytical method used for measuring barium in blood, urine and bone of humans and animals at ppt (sub μg/L) levels (Mauras and Allain 1979; Schramel 1988; Shiraishi et al. 1987). NAA technique has also been employed for measuring barium in blood of humans and animals at ppb (μg/L) levels (Olehy et al. 1966). These techniques are sensitive for measuring background levels of barium in the population. However, information is needed on whether data collected using these techniques can be used to correlate the levels of barium in biological tissues and fluids with exposure levels.

Effect. At present, no biomarkers of effect are available for barium. There are no data to indicate whether a biomarker, if available, would be preferred over chemical analysis for monitoring effects from long- and short-term exposure to barium.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. GFAAS and FAAS are the most widely used analytical techniques for measuring barium and its compounds in air (NIOSH 1987), water (ASTM 2000; Edelbeck and West 1970; EPA 1974, 1994a, 1994b; Fagioli et al. 1988; Johnson et al. 1983; Pierce and Brown 1977; Roe and Froelich 1984), seawater and brackish water (ASTM 1999), waste water (EPA 1974, 1979, 1992, 1994b), rocks and minerals (Bano 1973), unused lubricating oil (Holding and Rowson 1975), soil (EPA 1978, 1996), and diagnostic meals (Sharp and Knevel 1971). The media of most concern for potential human exposure to barium is water. GFAAS and FAAS techniques are sensitive for measuring background levels of barium in aqueous media (Epstein and Zander 1979; Roe and Froelich 1984). However, it is not known whether

these techniques are sensitive for measuring levels of barium at which health effects might begin to occur. FAAS and GFAAS are the methods (Methods 208.1, 208.2, 7080, and 7081) recommended by EPA for detecting ppb levels of barium in water and waste water (EPA 1974, 1979, 1992, 1994c). GFAAS has also been employed to detect ppt levels of barium in aqueous media (Epstein and Zander 1979; Roe and Froelich 1984). ICP-MS and ICP-AES quantitative methods are increasing in use for routine analysis of barium at ppb levels and are capable of ppt levels of detection when ion chromatographic and other prepurification methods are used in sample preparation and analysis. Therefore, analytical methods are available that are sufficiently specific and sensitive to measure barium in the environment, and no data needs have been identified at this time.

7.3.2 Ongoing Studies

No ongoing studies regarding techniques for measuring and determining barium in biological and environmental samples were located.

8. REGULATIONS AND ADVISORIES

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

ATSDR has derived an intermediate-duration oral MRL of 0.2 mg barium/kg/day for barium. This MRL is based on a NOAEL of 65 mg barium/kg/day and a LOAEL of 115 mg barium/kg/day for increased kidney weight in female rats (NTP 1994) and an uncertainty factor of 100 (10 to account for animal to human extrapolation, and 10 for human variability) and modifying factor of 3 to account for the lack of an adequate developmental toxicity study

ATSDR has derived a chronic-duration oral MRL of 0.2 mg barium/kg/day for barium. The MRL is based on a $BMDL_{05}$ of 61 mg barium/kg/day for nephropathy in male mice (NTP 1994) and an uncertainty factor of 100 (10 to account for animal to human extrapolation and 10 for human variability) and modifying factor of 3 to account for the lack of an adequate developmental toxicity study.

EPA (IRIS 2006) has derived an oral reference dose (RfD) for barium of 0.2 mg/kg/day, based on a $BMDL_{05}$ of 63 mg/kg/day for nephropathy in male mice (NTP 1994) and an uncertainty factor of 300 (10 to account for animal to human extrapolation, 10 for human variability, and 3 for database deficiencies, particularly the lack of a two-generation reproductive toxicity study and an adequate investigation of developmental toxicity). EPA (IRIS 2006) has not recommended an inhalation reference concentration (RfC) for barium at this time.

Using their 1986 guidelines, EPA has determined that barium is not classifiable as a human carcinogen and has assigned it the cancer classification, Group D (IRIS 2006). Using their recent guidelines, EPA determined that barium is considered not likely to be carcinogenic to humans following oral exposure and its carcinogenic potential cannot be determined following inhalation exposure (IRIS 2006).

Table 8-1. Regulations and Guidelines Applicable to Barium and Barium Compounds

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	No data	IARC 2004
WHO	Air quality guidelines	No data	WHO 2000
	Drinking water quality guidelines	0.7 mg/L	WHO 2004
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (TWA)		ACGIH 2004
	Barium and soluble compounds (as Ba)	0.5 mg/m^3	
	Barium sulfate	10 mg/m^3	
NIOSH	REL (TWA)		NIOSH 2005a, 2005b
	Barium chloride[a]	0.5 mg/m^3	
	Barium sulfate	10 mg/m^3 (total) 5.0 mg/m^3 (respiratory)	
	IDLH		
	Barium chloride	50 mg/m^3	
	Barium sulfate	No data	
OSHA	PEL (8-hour TWA) for general industry		OSHA 2005c 29 CFR 1910.1000
	Barium, soluble compounds (as Ba)	0.5 mg/m^3	
	Barium sulfate	15 mg/m^3 (total dust) 5.0 mg/m^3 (respirable fraction)	
	PEL (8-hour TWA) for construction industry		OSHA 2005b 29 CFR 1926.55
	Barium, soluble compounds (as Ba)	0.5 mg/m^3	
	PEL (8-hour TWA) for shipyard industry		OSHA 2005a 29 CFR 1915.1000
	Barium, soluble compounds (as Ba)	0.5 mg/m^3	
	Barium sulfate	15 mg/m^3 (total dust) 5.0 mg/m^3 (respirable fraction)	
b. Water			
EPA	Drinking water standards and health advisories		EPA 2004
	1-day health advisory for a 10-kg child	0.7 mg/L	
	10-day health advisory for a 10-kg child	0.7 mg/L	

Table 8-1. Regulations and Guidelines Applicable to Barium and Barium Compounds

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
	National primary drinking water standards		EPA 2002a
	MCLG	2.0 mg/L	
	MCL	2.0 mg/L	
	Reportable quantities of hazardous substances (barium cyanide) designated pursuant to Section 311 of the Clean Water Act	10 pounds	EPA 2005b 40 CFR 117.3
	Water quality criteria for human health consumption of:		EPA 2002b
	Water + organism	1.0 mg/L	
	Organism only	No data	
c. Food			
FDA	Bottled drinking water	2.0 mg/L	FDA 2004 21 CFR 165.110
d. Other			
ACGIH	Carcinogenicity classification	A4[b]	ACGIH 2004
EPA	Carcinogenicity classification	Group D[c]	IRIS 2006
	RfC	Not recommended at this time	
	RfD	0.2 mg/kg/day	
NTP	Carcinogenicity classification	No data	NTP 2005

[a]The REL also applies to other soluble barium compounds (as Ba) except barium sulfate.
[b]A4: not classifiable as a human carcinogen
[c]Group D: not classifiable as to human carcinogenicity

ACGIH = American Conference of Governmental Industrial Hygienists; CFR = Code of Federal Regulations; DWEL = drinking water equivalent level; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit values; TWA = time-weighted average; WHO = World Health Organization

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10. GLOSSARY

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

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

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

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

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

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

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

Biomarkers—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

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

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that 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.

10. GLOSSARY

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 of people that 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.

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

Immunological Effects—Functional changes in the immune response.

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.

***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 that 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 that has been calculated to cause death in 50% of a defined experimental animal population.

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

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

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

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

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

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

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

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

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

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

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

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

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that 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 OR of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

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

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

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

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

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

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

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar

ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

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

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

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

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

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

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL, from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

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

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

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

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

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

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

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

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

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

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

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

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

Toxic Dose$_{(50)}$ (TD$_{50}$)—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic—The 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 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis, 3 being the approximate logarithmic average of 10 and 1.

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

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

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

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

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

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

are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold 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 and Environmental Medicine, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Environmental Medicine, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Barium, Soluble Salts
CAS Numbers:
Date: August 2007
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 23
Species: Rat

Minimal Risk Level: 0.2 [X] mg/kg/day [ ] ppm

Reference: NTP. 1994. Toxicology and carcinogenesis studies of barium chloride dihydrate (CAS No. 10326-27-9) in F344/N rats and B6C3F1 mice (drinking water studies). Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Toxicology Program. NTP TR 432.

Experimental design: Groups of 10 male and 10 female F344/N rats were administered 0, 125, 500, 1,000, 2,000, or 4,000 ppm barium chloride dihydrate in drinking water for 90 days. Using measured body weights and water consumption, the investigators estimated the daily barium doses to be 0, 10, 30, 65, 110, and 200 mg barium/kg/day for males and 0, 10, 35, 65, 115, and 180 mg barium/kg/day for females. Neurobehavioral tests (spontaneous motor activity, grip strength, tail flick latency, startle response, hindlimb foot splay) were performed prior to exposure and after 45 and 90 days of exposure. Cardiovascular testing (heart rate, blood pressure, and electrocardiogram) was conducted prior to exposure and after 45 and 91 days of exposure. Organ weights (adrenal gland, brain, heart, liver, kidney, lung, testis, thymus), blood analysis for hematological and clinical chemistry (barium, sodium, potassium, calcium, and phosphorus levels) alterations, and histological examination of major tissues and organs (only in the 200/180 mg/kg/day group) were conducted at termination; kidney, liver, spleen, and thymus of male and female rats in the 110/115 mg/kg/day groups and adrenal gland, heart, and salivary gland of female rats in the 115 mg/kg/day group were also examined microscopically.

Effect noted in study and corresponding doses: Exposure-related deaths were observed during the last week in 30% of the males and 10% of the females exposed to 200/180 mg barium/kg/day. Significant decreases in final body weights were also observed in the 200 mg barium/kg/day males (13% lower than controls) and 180 mg barium/kg/day females (8% lower than controls); significant decreases in water consumption (approximately 30% lower than controls) were also observed at this dose level. Marginal, but statistically significant, decreases in undifferentiated motor activity was observed in all groups of rats exposed to barium for 90 days, except females exposed to 115 mg barium/kg/day; no other alterations in neurobehavioral performance were observed. No significant alterations in heart rate, blood pressure, or EKG readings were observed. Significant increases in serum phosphorus levels were observed in males in the 110 and 200 mg barium/kg/day groups and females in the 35, 65, 115, and 180 mg barium/kg/day groups; however, the investigators noted that these increases were probably an artifact from hemolysis of collected blood samples. Significant increases in absolute and relative kidney weights were observed in females exposed to 115 or 180 mg barium/kg/day and increases in relative kidney weights were also observed in males at 200 mg barium/kg/day. An increase in relative kidney weight was also observed in the females exposed to 65 mg barium/kg/day. The magnitude of the increases in relative kidney weights were 7, 14, and 19% in the females exposed to 65, 115, and 180 mg barium/kg/day and 12% in males exposed to 200 mg barium/kg/day. ;Minimal to mild, focal to multifocal dilatation of the proximal convoluted tubules of the outer medulla and renal cortex was observed in three male and three female rats in the 200/180 mg barium/kg/day group. The small increase in relative kidney weight (7%) observed in

the female rats exposed to 65 mg barium/kg/day was not considered biologically significant because it is not supported by an increase in histological alterations in the kidney at 65 or 115 mg barium/kg/day or in rats exposed to 75 mg barium/kg/day for 2 years (NTP 1994).

Dose and end point used for MRL derivation: The MRL is based on a NOAEL of 65 mg barium/kg/day for increased absolute and relative kidney weight. The increased kidney weight was considered an early indicator of potentially more serious effects in the kidney. A NOAEL/LOAEL approach was used to derive the MRL because none of the available benchmark dose models provided an adequate fit to the absolute or relative kidney weight data.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation: 100

[ ] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Modifying Factor used in MRL derivation: 3

[X] 3 for database deficiences

A modifying factor of 3 was included to account for deficiencies in the oral toxicity database, particularly the need for an additional developmental toxicity study. Decreases in pup birth weight and a nonstatistically significant decrease in live litter size were observed in the offspring of rats exposed to 180/200 mg Ba/kg/day as barium chloride in drinking water prior to mating (Dietz et al. 1992). Maternal body weight gain and water consumption were not reported, thus it is not known if the decreases in pup body weight were secondary to maternal toxicity or direct effect on the fetus. No developmental effects were observed in mice at the highest dose tested (200 mg Ba/kg/day) (Dietz et al. 1992). One other study examined the potential for developmental toxicity in orally exposed animals (Tarasenko et al. 1977). However, because the study was poorly reported and no incidence data or statistical analysis were presented in the published paper, the reported findings of increased mortality and systemic toxicity in the offspring of an unspecified species orally exposed to barium during conception and pregnancy can not be adequately evaluated. The Dietz et al. (1992) study was designed to be a mating trial and did not expose the animals during gestation; thus, database is lacking an adequate study to evaluate the potential for barium to induce developmental effects.

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No. Doses were calculated by the investigators using measured drinking water consumption and body weight data.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: There are limited data on the toxicity of barium in humans following repeated doses. Wones et al. (1990) found no significant alterations in blood pressure or ECG readings, relative to initial baseline measurements in men experimentally exposed to up to 0.2 mg barium/kg/day as barium chloride in drinking water for 4 week (Wones et al. 1990). These findings are supported by several animal studies that did not find significant

alterations in blood pressure or ECG readings in rats exposed to 150–180 mg barium/kg/day in drinking water for 13 or 16 weeks, respectively (McCauley et al. 1985; NTP 1994). A study by Perry et al. (1983, 1985, 1989) found significant increases in blood pressure in rats administered 8.6 or 11 mg barium/kg/day as barium chloride in drinking water for 1 or 4 months, respectively. The reason for the differences between the results from the Perry et al. (1983, 1985, 1989) study and the NTP (1994) and McCauley et al. (1985) studies is not known. It is possible that the diet used in the Perry et al. (1983, 1985, 1989) study influenced the results. In this study, the rats were fed a low-mineral diet; the calcium content of the rye-based diet was 3.8 mg/kg, which is lower than the concentration recommended for maintenance, growth, and reproduction of laboratory rats (NRC 1995b).

The results of studies by McCauley et al. (1985) and NTP (1994) suggest that the kidney is the most sensitive target of toxicity in rats and mice. In the McCauley et al. (1985) study, glomerular alterations consisting of fused podocytes and thickening of the capillary basement membrane were found in rats exposed to 150 mg barium/kg/day in drinking water for 16 weeks. This lesion was found in uninephrectomized Sprague Dawley rats, Dahl salt-sensitive rats, and Dahl salt-resistant rats. In the NTP (1994) rat study, significant increases in absolute and relative kidney weights were observed in female rats exposed to 115 or 180 mg barium/kg/day and in males exposed to 200 mg barium/kg/day. A statistically significant increase in relative kidney weight was also observed in the females exposed to 65 mg barium/kg/day; however, the increase was small (7%) and was not considered biologically significant. At 200 and 180 mg barium/kg/day, minimal to mild dilatation of the proximal renal cortex was observed in the males and females, respectively; an increase in mortality (30%) was also observed in the males exposed to 200 mg barium/kg/day. In mice, mild to moderate nephropathy (characterized as tubule dilatation, regeneration, and atrophy) was observed in 100% of the males exposed to 450 mg barium/kg/day and 90% of the females exposed to 495 mg barium/kg/day; no renal lesions were observed at the next lowest dose level (205 and 200 mg barium/kg/day in males and females, respectively). Other effects observed at the 450/495 mg barium/kg/day dose level included weight loss, spleen and thymus atrophy, and increased mortality (60% of the males and 70% of females died after 5 weeks of exposure).

Other end points that have been examined in rats and mice include neurotoxicity, reproductive toxicity, and developmental toxicity. In male and female rats, slight decreases in undifferentiated motor activity were observed at 10 mg barium/kg/day and higher. However, with the exception of female rats exposed to 200 mg barium/kg/day, the difference between motor activity in the barium-exposed rats and the controls was less than 20%; this was not considered to be biologically significant. At 200 mg barium/kg/day, the difference was 30%, which was considered to be adverse. No significant alterations were found in performance on the remaining neurobehavioral tests (grip strength, tail flick latency, startle response, and hindlimb foot splay). In mice, a significant decrease in forelimb grip strength was observed in females exposed to 495 mg barium/kg/day; this may have been due to debilitation. No other alterations in neurobehavioral performance were found. No effects on reproductive tissues or reproductive performance were observed in rats or mice exposed to approximately 200 mg barium/kg/day (Dietz et al. 1992; NTP 1994). Pre-mating exposure to 180/200 mg barium/kg/day resulted in decreased litter size and body weight in rat offspring; the NOAEL for these effects was 110/115 mg barium/kg/day (Dietz et al. 1992). No developmental effects were observed in mice exposed to 200 mg barium/kg/day (Dietz et al. 1992).

Agency Contacts (Chemical Managers): Cassandra Smith and Yee-Wan Stevens

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Barium, Soluble Salts
CAS Numbers:
Date: August 2007
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 49
Species: Mouse

Minimal Risk Level: 0.2 [X] mg barium/kg/day [ ] ppm

Reference: NTP. 1994. Toxicology and carcinogenesis studies of barium chloride dihydrate (CAS No. 10326-27-9) in F344/N rats and B6C3F1 mice (drinking water studies). U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Toxicology Program, Research Triangle Park, NC. NTP TR 432.

Experimental design: Groups of 60 male and 60 female B6C3F1 mice were administered 0, 500, 1,250, or 2,500 ppm barium chloride dehydrate in drinking water for 2 years. Using measured body weights and water consumption, the investigators estimated the daily barium doses to be 0, 30, 75, and 160 mg barium/kg/day for males and 0, 40, 90, and 200 mg barium/kg/day for females. Organ weights, blood analysis for hematological and clinical chemistry (barium, sodium, potassium, calcium, and phosphorus levels, and alanine aminotransferase, creatine kinase, lactate dehydrogenase, and gamma-glutamyltransferase activities) alterations (measured after 15 months), and histological examination of major tissues and organs were conducted at termination.

Effect noted in study and corresponding doses: Increased mortality attributed to renal lesions was observed in the 160/200 mg/kg/day group. Decreased body weights (<7%) were observed in the barium-exposed mice. The investigators noted that a moderate to marked weight loss was observed in animals dying early. No significant alterations in hematology or clinical chemistry parameters were observed. A significant increase in the incidence of nephropathy was observed in male and female mice exposed to 160/200 mg/kg/day. The nephropathy was characterized by extensive regeneration of cortical and medullary tubule epithelium, tubule dilatation, hyaline cast formation, multifocal interstitial fibrosis, and glomerulosclerosis in some kidneys. The incidence of nephropathy was 1/50, 0/50, 2/48, and 19/50 in the males and 0/50, 2/53, 1/50, and 37/50 in the females, respectively. The average severity of the nephropathy was 3.6 (moderate to marked) for both the males and females in the 160/200 mg/kg/day group. An increased incidence of lymphoid depletion in the spleen and decreased relative and absolute spleen were also observed in the 160/200 mg/kg/day group; however, this was attributed to debilitation associated with nephropathy rather than a direct effect on the spleen. No significant increases in the incidences of neoplasms were observed.

Dose and end point used for MRL derivation: Benchmark dose analysis of the dose-response data (Table A-1) for nephropathy in male and female mice exposed to barium chloride in drinking water for 2 years (NTP 1994) was conducted. EPA's Benchmark Dose Software (version 1.3.2) was used to fit nine mathematical models to the incidence data. Model fit was judged by the p-values associated with the chi-square goodness-of-fit statistic generated by the models and visual inspection of the plot of observed and predicted values. As assessed by the chi-square goodness-of-fit test, several models in the software provided adequate fits to the data for the incidence of nephropathy in male and female mice (x^2 p-value $\geq$0.1). As assessed by lowest Akaike Information Criterion (AIC), the logistic model for the male mouse

data and the gamma model for the female mouse data provide the greatest fit. The results of the benchmark dose analysis are presented in Table A-2.

Table A-1. Incidence of Nephropathy in Male and Female Mice Exposed to Barium Chloride in Drinking Water for 2 Years (NTP 1994)

Water concentration (ppm)	Dose (mg barium/kg/day)	Incidence
Males		
0	0	1/50
500	30	0/50
1,250	75	2/48
2,500	160	19/50
Females		
0	0	0/50
500	40	2/53
1,250	90	1/50
2,500	200	37/50

Table A-2. Predictions from Models for Doses Associated with 10 and 5% Extra Risk for the Incidence of Nephropathy in Male and Female Mice Exposed to Barium in Drinking Water for 2 Years (NTP 1994)

Model	BMD_{10} mg/kg/day	$BMDL_{10}$ mg/kg/day	BMD_5 mg/kg/day	$BMDL_5$ mg/kg/day	x^2 p-value	AIC
Male mice						
Logistic	**103.96**	**87.26**	**80.06**	**61.13**	**0.28**	**99.34**
Probit	96.13	80.07	71.96	54.66	0.13	100.11
Log-probit[a]	99.73	77.90	83.39	59.54	0.31	100.25
Gamma[b]	102.31	80.06	84.94	59.65	0.31	100.28
Log-logistic[a]	104.44	80.50	86.43	59.69	0.31	100.32
Weibull[b]	106.59	81.79	87.63	59.54	0.31	100.35
Quantal quadratic	82.83	69.51	57.80	48.5	0.14	101.89
Multi-stage[c]	82.83	69.14	57.80	44.97	0.14	101.89
Quantal linear	NA	NA	NA	NA	0.0032	111.94
Female mice						
Gamma[b]	125.59	101.49	113.96	87.66	0.34	90.89
Log-probit[a]	134.85	100.63	125.10	88.39	0.17	92.84
Log-logistic[a]	147.43	101.75	137.35	87.01	0.17	92.84
Weibull[b]	153.60	102.66	142.51	84.95	0.17	92.84
Logistic	NA	NA	NA	NA	0.08	92.35

Table A-2. Predictions from Models for Doses Associated with 10 and 5% Extra Risk for the Incidence of Nephropathy in Male and Female Mice Exposed to Barium in Drinking Water for 2 Years (NTP 1994)

Model	BMD_{10} mg/kg/day	$BMDL_{10}$ mg/kg/day	BMD_5 mg/kg/day	$BMDL_5$ mg/kg/day	x^2 p-value	AIC
Probit	NA	NA	NA	NA	0.03	94.03
Quantal quadratic	NA	NA	NA	NA	0.01	102.21
Multi-stage[c]	NA	NA	NA	NA	0.01	102.21
Quantal linear	NA	NA	NA	NA	0.00	126.61

[a]slope restricted to >1
[b]restrict power ≥1
[c]restrict betas ≥0

degree of polynomial = 2; NA = not applicable

The $BMDL_{05}$ for male mice was selected as the point of departure for deriving the chronic-duration oral MRL. Data from the male mice were used because they identify a lower BMDL than the female data. The predicted 5% incidence approach was selected over the other two approaches as a precaution due to the severity of the observed effects (moderate to marked severity nephropathy), which resulted in marked weight loss and increased mortality.

[ ] NOAEL [ ] LOAEL [X] BMDL

Uncertainty Factors used in MRL derivation: 300

[ ] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Modifying Factor used in MRL derivation: 3

[X] 3 for database deficiences

A modifying factor of 3 was included to account for deficiencies in the oral toxicity database, particularly the need for an additional developmental toxicity study. Decreases in pup birth weight and a nonstatistically significant decrease in live litter size were observed in the offspring of rats exposed to 180/200 mg Ba/kg/day as barium chloride in drinking water prior to mating (Dietz et al. 1992). Maternal body weight gain and water consumption were not reported, thus it is not known if the decreases in pup body weight were secondary to maternal toxicity or direct effect on the fetus. No developmental effects were observed in mice at the highest dose tested (200 mg Ba/kg/day) (Dietz et al. 1992). One other study examined the potential for developmental toxicity in orally exposed animals (Tarasenko et al. 1977). However, because the study was poorly reported and no incidence data or statistical analysis were presented in the published paper, the reported findings of increased mortality and systemic toxicity in the offspring of an unspecified species orally exposed to barium during conception and pregnancy can not be adequately evaluated. The Dietz et al. (1992) study was designed to be a mating trial and did not expose

the animals during gestation; thus, database is lacking an adequate study to evaluate the potential for barium to induce developmental effects.

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No. Doses were calculated by the investigators using measured drinking water consumption and body weight data.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: Several studies have examined the toxicity of barium following chronic-duration exposure. Significant increases in blood pressure were observed in rats exposed to 0.8 mg barium/kg/day as barium chloride in drinking water for 16 months (Perry et al. 1983, 1985, 1989); the NOAEL for this effect was 0.17 mg barium/kg/day. At higher doses (7.2 mg barium/kg/day), depressed rates of cardiac contraction, reduced cardiac electrical conductivity, and decreased cardiac ATP levels were observed. As noted in the discussion of the intermediate-duration oral MRL, interpretation of the results of this study is limited due to the low mineral diet which may have supplied inadequate levels of calcium.

No adverse effects were observed in rats exposed to 60 mg barium/kg/day as barium chloride in drinking water for 2 years (NTP 1994), 15 mg barium/kg/day to an unspecified barium compound in drinking water for 68 weeks (McCauley et al. 1985), or 0.7 mg barium/kg/day as barium acetate in drinking water for a lifetime (Schroeder and Mitchener 1975a). In mice exposed to barium chloride in drinking water for 2 years, marked renal nephropathy was observed at 160 mg barium/kg/day; the increased incidence of nephropathy in the next lowest dose group (75 mg barium/kg/day) was not statistically significant. Other adverse effects observed at 160 mg barium/kg/day included weight loss and increased mortality.

The animal data provide suggestive evidence that the kidney is the most sensitive target of toxicity. A serious LOAEL of 160 mg barium/kg/day was identified for nephropathy in mice (NTP 1994); the NOAEL identified in this study is 75 mg/kg/day. Although no kidney lesions were observed in rats exposed to doses as high as 60 mg barium/kg/day (NTP 1994), the doses utilized in the study may not have been high enough to cause kidney damage. Biologically significant kidney alterations were observed at 115 mg barium/kg/day and higher in rats exposed for an intermediate duration (NTP 1994).

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APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

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

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

Chapter 2

Relevance to Public Health

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

1. What effects are known to occur in humans?

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

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

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

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

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

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived 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.

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

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

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

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (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 levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures 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, 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 NOAELs, LOAELs, or Cancer Effect Levels (CELs).

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

LEGEND

See Sample LSE Table 3-1 (page B-6)

(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. Typically when sufficient data exist, 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 Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

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

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

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

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

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens 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 “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 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, one systemic effect (respiratory) was investigated.

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

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

(11) CEL. A 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 that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

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 acute and intermediate exposure periods are illustrated.

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

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

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

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

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

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

SAMPLE

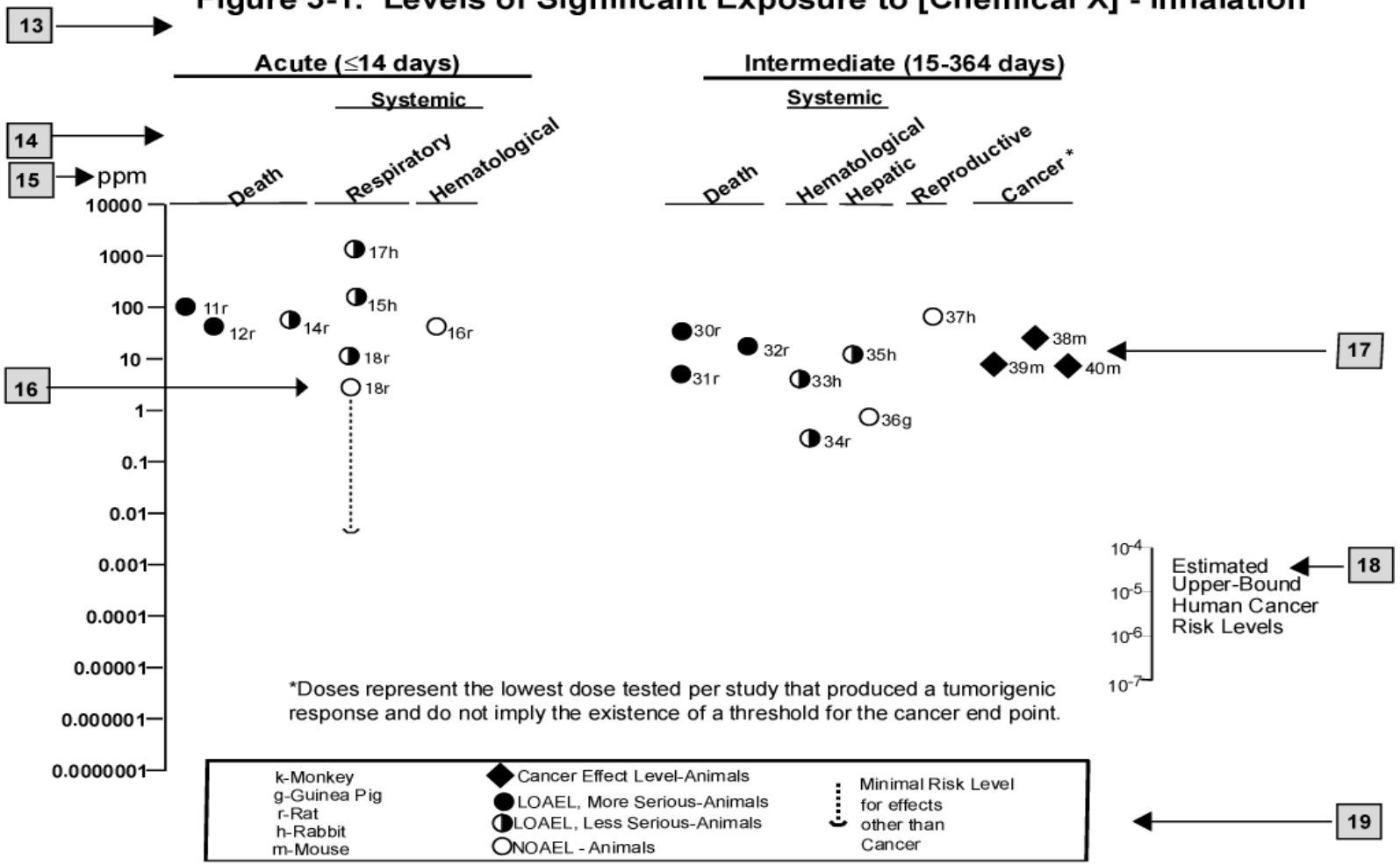
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

	Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	Serious (ppm)	Reference
2 →	INTERMEDIATE EXPOSURE							
		5	6	7	8	9		10
3 →	Systemic	↓	↓	↓	↓	↓		↓
4 →	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
	CHRONIC EXPOSURE							
	Cancer					11		
						↓		
	38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
	39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
	40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

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



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

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

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

MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
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
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
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
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

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

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APPENDIX D. INDEX