TOXICOLOGICAL PROFILE FOR ARSENIC

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

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UPDATE STATEMENT

Toxicological profiles are revised and republished as necessary, but no less than once every three years. For information regarding the update status of previously released profiles, contact ATSDR at:

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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:

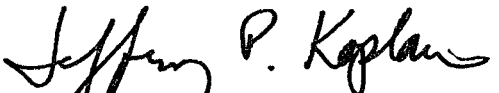
(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

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



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*Legislative Background

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

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

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

Chapter 2: Health Effects: Specific health effects of a given hazardous compound are reported by *route of exposure*, by *type of health effect* (death, systemic, immunologic, reproductive), and by *length of exposure* (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.

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

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

Section 1.6 How Can Arsenic Affect Children?
Section 1.7 How Can Families Reduce the Risk of Exposure to Arsenic?
Section 2.7 Children's Susceptibility
Section 5.6 Exposures of Children

Other Sections of Interest:

Section 2.8 Biomarkers of Exposure and Effect
Section 2.11 Methods for Reducing Toxic Effects

ATSDR Information Center

Phone: 1-888-42-ATSDR or (404) 639-6357 ***Fax:*** (404) 639-6359
E-mail: atsdric@cdc.gov ***Internet:*** http://www.atsdr.cdc.gov

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

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

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

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

Other Agencies and Organizations

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

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

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

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. *Contact:* AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: aoec@dgs.dgsys.com • AOEC Clinic Director: http://occ-env-med.mc.duke.edu/oem/aoec.htm.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. *Contact:* ACOEM, 55 West Seegers Road, Arlington Heights, IL 60005 • Phone: 847-228-6850 • FAX: 847-228-1856.

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

PEER REVIEW

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

1. Celia Evans, Exponent, Inc. 15375 SE 30th Place, Suite 250, Bellevue, Washington 98007;

2. Nicolas Bloom, Frontier Geosciences, 414 Pontius North "B", Seattle, Washington 98109; and

3. Ingeborg Harding-Barlow, Private Consultant, 3717 Laguna Ave., Palo Alto, California 94306.

These experts collectively have knowledge of arsenic's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about arsenic and the effects of exposure.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal cleanup activities. Arsenic has been found in at least 1,014 of the 1,598 current or former NPL sites. However, the total number of NPL sites evaluated for this substance is not known. As more sites are evaluated, the sites at which arsenic is found may increase. This information is important because exposure to this substance may harm you and because these sites may be sources of exposure.

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

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

1.1 WHAT IS ARSENIC?

Arsenic is an element that is widely distributed in the earth's crust. Elemental arsenic is ordinarily a steel grey metal-like material that sometimes occurs naturally. However, arsenic is usually found in the environment combined with other elements such as oxygen, chlorine, and sulfur. Arsenic combined with these elements is called inorganic arsenic. Arsenic combined with carbon and hydrogen is referred to as organic arsenic. Understanding the difference between inorganic and organic arsenic is important because the organic forms are usually less harmful than the inorganic forms.

Most inorganic and organic arsenic compounds are white or colorless powders that do not evaporate. They have no smell, and most have no special taste. Thus, you usually cannot tell if arsenic is present in your food, water, or air.

Inorganic arsenic occurs naturally in soil and in many kinds of rock, especially in minerals and ores that contain copper or lead. When these ores are heated in smelters, most of the arsenic goes up the stack and enters the air as a fine dust. Smelters may collect this dust and take out the arsenic as arsenic trioxide. However, arsenic is no longer produced in the United States; all the arsenic we use is imported.

Presently about 90% of all arsenic produced is used as a preservative for wood to make it resistant to rotting and decay. The preservative is chromated copper arsenate (CCA) and the treated wood is referred to as "pressure-treated." In the past, arsenic was primarily used as a pesticide, primarily on cotton fields and in orchards. Inorganic arsenic compounds can no longer be used in agriculture. However, organic arsenicals, namely cacodylic acid, disodium methyl-arsenate (DSMA), and monosodium methylarsenate (MSMA) are still used as pesticides, principally on cotton. Small quantities of arsenic metal are added to other metals forming metal mixtures or alloys with improved properties. The greatest use of arsenic in alloys is in lead-acid batteries used in automobiles. Another important use of arsenic compounds is in semiconductors and light-emitting diodes.

To learn more about the properties and uses of arsenic, see Chapters 3 and 4.

1.2 WHAT HAPPENS TO ARSENIC WHEN IT ENTERS THE ENVIRONMENT?

Arsenic occurs naturally in soil and minerals and therefore it may enter the air, water, and land from wind-blown dust and may get into water from runoff and leaching. Volcanic eruptions are another source of arsenic. Arsenic is associated with ores mined for metals, such as copper and lead, and may enter the environment during the mining and smelting of these ores. Small amounts of arsenic also may be released into the atmosphere from coal-fired power plants and incinerators because coal and waste products often contain some arsenic.

Arsenic cannot be destroyed in the environment. It can only change its form, or become attached or separated, from particles. It may change its form by reacting with oxygen or other molecules present in air, water, or soil, or by the action of bacteria that live in soil or sediment. Arsenic released from power plants and other combustion processes is usually attached to very small particles. Arsenic contained in wind-borne soil is generally found in larger particles. These particles settle to the ground or are washed out of the air by rain. Arsenic that is attached to very small particles may stay in the air for many days and travel long distances. Many common arsenic compounds can dissolve in water. Thus, arsenic can get into lakes, rivers, or underground water by dissolving in rain or snow or through the discharge of industrial wastes. Some of the arsenic will stick to particles in the water or sediment on the bottom of the lakes or river, and some will be carried along by the water. Ultimately most arsenic ends up in the soil or sediment. Although some fish and shellfish take in arsenic which may build up in tissues, most of this arsenic is in a form (often called "fish arsenic") that is less harmful.

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

1.3 HOW MIGHT I BE EXPOSED TO ARSENIC?

Arsenic is found naturally in the environment. You may be exposed to arsenic by eating food, drinking water, or breathing air. Children may also be exposed to arsenic by eating dirt. You may also be exposed by skin contact with soil or water that contains arsenic. Analytical methods used by scientists to determine the levels of arsenic in the environment generally do not determine the specific form of arsenic present. Therefore, we do not always know the form of arsenic a person may be exposed to. Similarly, we often do not know what forms of arsenic are present at hazardous waste sites. Some forms of arsenic may be so tightly attached to particles or embedded in minerals that they are not taken up by plants and animals.

The concentration of arsenic in soil varies widely, generally ranging from about 1 to 40 parts of arsenic to a million parts of soil (ppm) with an average level of 5 ppm. However soils in the vicinity of arsenic-rich geological deposits, some mining and smelting sites, or agricultural areas where arsenic pesticides had been applied in the past may contain much higher levels of arsenic.

The concentration of arsenic in natural surface and groundwater is generally about 1 part in a billion parts of water (1 ppb) but may exceed 1,000 ppb in mining areas or where arsenic levels in soil are high. Groundwater is far more likely to contain high levels of arsenic than surface water. Surveys of U.S. drinking water indicate that about 80% of water supplies have less than 2 ppb of arsenic, but 2% of supplies exceed 20 ppb of arsenic. Levels of arsenic in food range from about 20 to 140 ppb. However, levels of inorganic arsenic, the form of most concern, are far lower. Levels of arsenic in the air generally range from less than 1 to about 2,000 nanograms (1 nanogram equals a billionth of a gram) of arsenic per cubic meter of air (less than 1–2,000 ng/m^3), depending on location, weather conditions, and the level of industrial activity in the area. However urban areas generally have mean arsenic levels in air ranging from 20 to 30 ng/m^3, most of which is attached to small particles.

You normally take in small amounts of arsenic in the air you breathe, the water you drink, and the food you eat. Of these, food is usually the largest source of arsenic. Fish and seafood contain the greatest amounts of arsenic, but this is mostly the organic form of arsenic that is less harmful. Children are likely to eat small amounts of dust or dirt each day, so this is another way they may be exposed to arsenic. The total amount of arsenic you take in from these sources is generally about 50 µg each day. The level of inorganic arsenic (the form of most concern) you take in from these sources is generally about 3.5 µg/day.

In addition to the normal levels of arsenic in air, water, soil, and food, you could be exposed to higher levels in several ways, such as the following:

- Some areas of the United States contain unusually high natural levels of arsenic in rock, and this can lead to unusually high levels of arsenic in soil or water. If you live in an area like this, you could take in elevated amounts of arsenic in drinking water. Children may be taking in arsenic because of hand to mouth contact or eating dirt.

- Some hazardous waste sites contain large quantities of arsenic. If the material is not properly disposed of, it can get into surrounding water, air, or soil. If you live near such a site, you could be exposed to elevated levels of arsenic from these media.

- If you work in an occupation that involves arsenic production or use (for example, copper or lead smelting, wood treating, pesticide application), you could be exposed to elevated levels of arsenic during your work.

- If you saw or sand arsenic-treated wood, you could inhale some of the sawdust into your nose or throat. Similarly, if you burn arsenic-treated wood, you could inhale arsenic in the smoke.

- If you live in a formerly agricultural area where arsenic was used on crops, the soil could contain high levels of arsenic.

- In the past, several kinds of products used in the home (rat poison, ant poison, weed killer, some types of medicines) had arsenic in them. However, most of these uses of arsenic have ended, so you are not likely to be exposed from home products any longer.

You can find more information on how you may be exposed to arsenic in Chapter 5.

1.4 HOW CAN ARSENIC ENTER AND LEAVE MY BODY?

If you swallow arsenic in water, soil, or food, most of the arsenic may quickly enter into your body. The amount that enters your body will depend on how much you swallow and the kind of arsenic that you swallow. This is the most likely way for you to be exposed near a waste site. If you breathe air that contains arsenic dusts, many of the dust particles settle onto the lining of the lungs. Most of the arsenic in these particles is then taken up from the lungs into the body. You might be exposed in this way near waste sites where arsenic-contaminated soils are allowed to blow into the air. If you get arsenic-contaminated soil or water on your skin, only a small amount will go through your skin into your body, so this is usually not of concern.

If you are exposed to arsenic, your liver changes some of this to a less harmful organic form. Both inorganic and organic forms leave your body in your urine. Most of the arsenic will be gone within several days, although some will remain in your body for several months or even longer.

You can find more information on how arsenic enters and leaves your body in Chapter 2.

1.5 HOW CAN ARSENIC AFFECT MY HEALTH?

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

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

Inorganic arsenic has been recognized as a human poison since ancient times, and large oral doses (above 60,000 ppb in food or water) can produce death. If you swallow lower levels of inorganic arsenic (ranging from about 300 to 30,000 ppb in food or water), you may experience irritation of your stomach and intestines, with symptoms such as stomach ache, nausea, vomiting, and diarrhea. Other effects you might experience from swallowing inorganic arsenic include decreased production of red and white blood cells which may cause fatigue, abnormal heart rhythm, blood-vessel damage resulting in bruising, and impaired nerve function causing a "pins and needles" sensation in your hands and feet.

Perhaps the single most characteristic effect of long-term oral exposure to inorganic arsenic is a pattern of skin changes. These include a darkening of the skin and the appearance of small "corns" or "warts" on the palms, soles, and torso. A small number of the corns may ultimately develop into skin cancer. Swallowing arsenic has also been reported to increase the risk of cancer in the liver, bladder, kidneys, prostate, and lungs. The Department of Health and Human Services (DHHS) has determined that inorganic arsenic is a known carcinogen. The International Agency for Research on Cancer (IARC) has determined that inorganic arsenic is carcinogenic to humans. Both the EPA and the National Toxicology Program (NTP) have classified inorganic arsenic as a known human carcinogen.

If you breathe high levels of inorganic arsenic, you are likely to experience a sore throat and irritated lungs. You may also develop some of the skin effects mentioned above. The exposure level that produces these effects is uncertain, but it is probably above 100 micrograms of arsenic per cubic meter ($\mu g/m^3$) for a brief exposure. Longer exposure at lower concentrations can lead to skin effects, and also to circulatory and peripheral nervous disorders. There are some data suggesting that inhalation of inorganic arsenic may also interfere with normal fetal development, although this is not certain. An important concern is the ability of inhaled inorganic arsenic to increase the risk of lung cancer. This has been seen mostly in workers exposed to arsenic at smelters, mines, and chemical factories, but also in residents living near smelters and arsenical chemical factories. People who live near waste sites with arsenic may have an increased risk of lung cancer as well.

If you have direct skin contact with inorganic arsenic compounds, your skin may become irritated, with some redness and swelling. However, it does not appear that skin contact is likely to lead to any serious internal effects.

Despite all the adverse health effects associated with inorganic arsenic exposure, there is some evidence that the small amounts of arsenic in the normal diet (10–50 ppb) may be beneficial to your health. For example, animals fed a diet with unusually low concentrations of arsenic did not gain weight normally. They also became pregnant less frequently than animals fed a diet containing a normal amount of arsenic. Further, the offspring from these animals tended to be smaller than normal, and some died at an early age. However, no cases of arsenic deficiency in humans have ever been reported.

Almost no information is available on the effects of organic arsenic compounds in humans. Studies in animals show that most simple organic arsenic compounds (such as methyl and dimethyl compounds) are less toxic than the inorganic forms and that some complex organic arsenic compounds are virtually non-toxic. However, high doses can produce some of the same effects. Thus, if you are exposed to high doses of an organic arsenic compound, you might develop nerve injury, stomach irritation, or other effects, but this is not known for certain.

You can find more information on the health effects of inorganic and organic arsenic in Chapter 2.

1.6 HOW CAN ARSENIC AFFECT CHILDREN?

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

Children are exposed to arsenic in many of the same ways that adults are. Since arsenic is found in the soil, water, food, and air, children may take in arsenic in the air they breathe, the water they drink, and the food they eat. Since children tend to eat or drink less of a variety of foods and beverages than do adults, ingestion of contaminated food or juice or infant formula made with arsenic-contaminated water may represent a significant source of exposure. In addition, since children often play in the dirt and put their hands in their mouths and sometimes intentionally eat dirt, ingestion of contaminated soil may be a more important source of arsenic exposure for children than for adults. In areas of the United States where natural levels of arsenic in the soil and water are high, or in areas in and around contaminated waste sites, exposure of children to arsenic through ingestion of soil and water may be significant. In addition, contact with adults who are wearing clothes contaminated with arsenic (e.g., with dust from copper- or lead-smelting factories, from wood-treating or pesticide application, or from arsenic-treated wood) could be a source of exposure. Because of the tendency of children to taste things that they find, accidental poisoning from ingestion of pesticides is also a possibility. Thus, although most of the exposure pathways for children are the same as those for adults, children may be at a higher risk of exposure because of their lack of consistent hygiene practices and their curiosity about unknown powders and liquids.

Children who are exposed to arsenic may have many of the same effects as adults, including irritation of the stomach and intestines, blood vessel damage, skin changes, and reduced nerve function. Thus, all health effects observed in adults are of potential concern in children. We do not know if absorption of arsenic from the gut in children differs from adults. There is some information suggesting that children may be less efficient at converting inorganic arsenic to the

less harmful organic forms. For this reason, children may be more susceptible to health effects from inorganic arsenic than adults.

At present, there is no convincing evidence that inhaled or ingested arsenic can injure pregnant women or their fetuses, although studies in animals show that large doses of arsenic that cause illness in pregnant females can also cause low birth weight, fetal malformations, and even fetal death. Arsenic can cross the placenta and has been found in fetal tissues. Arsenic is found at low levels in breast milk.

You can find more information about how arsenic can affect children in Sections 2.7 and 5.6.

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

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

If you use arsenic-treated wood in home projects, personal protection from exposure to arsenic-containing sawdust may be helpful in limiting exposure of family members. These measures may include dust masks, gloves, and protective clothing. If you live in an area with a high level of arsenic in the water or soil, substituting cleaner sources of water and limiting contact with soil (for example, through use of a dense groundcover or thick lawn) would reduce family exposure to arsenic. By paying careful attention to dust and dirt control in the home (air filters, frequent cleaning), you can reduce family exposure to contaminated dirt. Some children eat a lot of dirt. You should prevent your children from eating dirt. You should discourage your children from putting objects in their mouths. Make sure they wash their hands frequently and before eating. Discourage your children from putting their hands in their mouths or other hand-to-mouth activity. Since arsenic may be found in the home as a pesticide, household chemicals containing arsenic should be stored out of reach of young children to prevent accidental poisonings. Always store household chemicals in their original labeled containers; never store household

chemicals in containers children would find attractive to eat or drink from, such as old soda bottles. Keep your Poison Control Center's number by the phone.

It is sometimes possible to carry arsenic from work on your clothing, skin, hair, tools, or other objects removed from the workplace. This is particularly likely if you work in the fertilizer, pesticide, glass, or copper/lead smelting industries. You may contaminate your car, home, or other locations outside work where children might be exposed to arsenic. You should know about this possibility if you work with arsenic.

Your occupational health and safety officer at work can and should tell you whether chemicals you work with are dangerous and likely to be carried home on your clothes, body, or tools and whether you should be showering and changing clothes before you leave work, storing your street clothes in a separate area of the workplace, or laundering your work clothes at home separately from other clothes. Material safety data sheets (MSDS) for many chemicals used should be found at your place of work, as required by the Occupational Safety and Health Administration (OSHA) in the U.S. Department of Labor. MSDS information should include chemical names and hazardous ingredients, and important properties, such as fire and explosion data, potential health effects, how you get the chemical(s) in your body, how to properly handle the materials, and what to do in the case of emergencies. Your employer is legally responsible for providing a safe workplace and should freely answer your questions about hazardous chemicals. Your state OSHA-approved occupational safety and health program or U.S. OSHA can answer any further questions and help your employer identify and correct problems with hazardous substances. Your state OSHA-approved occupational safety and health program or U.S. OSHA will listen to your formal complaints about workplace health hazards and inspect your workplace when necessary. Employees have a right to seek safety and health on the job without fear of punishment.

You can find more information about how arsenic can affect children in Sections 2.7 and 5.6.

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

Several sensitive and specific tests can measure arsenic in your blood, urine, hair, or fingernails, and these tests are often helpful in determining if you have been exposed to above-average levels of arsenic. These tests are not usually performed in a doctor's office. They require sending the sample to a testing laboratory.

Measurement of arsenic in your urine is the most reliable means of detecting arsenic exposures that you experienced within the last several days. Most tests measure the total amount of arsenic present in your urine. Sometimes this can be misleading, because the nonharmful forms of arsenic in fish and shellfish can give a high reading even if you have not been exposed to a toxic form of arsenic. For this reason, laboratories sometimes use a more complicated test to separate "fish arsenic" from other forms. Because most arsenic leaves your body within a few days, analysis of your urine cannot detect if you were exposed to arsenic in the past. Tests of your hair or fingernails can tell if you were exposed to high levels over the past 6–12 months, but these tests are not very useful in detecting low-level exposures. If high levels of arsenic are detected, this shows that you have been exposed, but unless more is known about when you were exposed and for how long, it is usually not possible to predict whether you will have any harmful health effects.

You can find more information on how arsenic can be measured in your hair, urine, nails, and other tissues in Chapters 2 and 6.

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

The federal government develops regulations and recommendations to protect public health. Regulations can be enforced by law. Federal agencies that develop regulations for toxic substances include the Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA).

Recommendations provide valuable guidelines to protect public health but cannot be enforced by law. Federal organizations that develop recommendations for toxic substances include the Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH).

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

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

The federal government has taken several steps to protect humans from arsenic. First, EPA has set limits on the amount of arsenic that industrial sources can release into the environment. Second, EPA has restricted or canceled many of the uses of arsenic in pesticides and is considering further restrictions. Third, EPA has set a limit of 50 ppb for arsenic in drinking water. EPA has recently proposed lowering this value to 5 ppb. Finally, OSHA has established a permissible exposure limit (PEL), 8-hour time-weighted average, of 10 $\mu g/m^3$ for airborne arsenic in various workplaces that use inorganic arsenic.

You can find more information on regulations and guidelines that apply to arsenic in Chapter 7.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department or

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

* Information line and technical assistance

Phone: 1-888-42-ATSDR (1-888-422-8737)
Fax: (404) 639-6359

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

* To order toxicological profiles, contact

National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161
Phone: (800) 553-6847 or (703) 605-6000

2. HEALTH EFFECTS

2.1 INTRODUCTION

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

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-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 (LOAEL) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of arsenic are indicated in Tables 2-1, 2-3, and 2-4 and Figures 2-1, 2-3, and 2-4. Because cancer effects could occur at lower exposure levels, Figure 2-3 also shows a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for arsenic. 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 1990i), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

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

Chemical Forms of Concern. Analysis of the toxic effects of arsenic is complicated by the fact that arsenic can exist in several different valence states and many different inorganic and organic compounds. Most cases of human toxicity from arsenic have been associated with exposure to inorganic arsenic, so these compounds are the main focus of this profile.

The most common inorganic arsenical in air is arsenic trioxide (As_2O_3), while a variety of inorganic arsenates (AsO_4^{-3}) or arsenites (AsO_2^-) occur in water, soil, or food. A number of studies have noted differences in the relative toxicity of these compounds, with trivalent arsenites tending to be somewhat more toxic than pentavalent arsenates (Byron et al. 1967; Gaines 1960; Maitani et al. 1987a; Sardana et al. 1981; Willhite 1981). However, these distinctions have not been emphasized in this profile, for several reasons: (1) in most cases, the differences in the relative potency are reasonably small (about 2–3-fold), often within the bounds of uncertainty regarding NOAEL or LOAEL levels; (2) different forms of arsenic may be interconverted, both in the environment (see Section 5.3) and the body (see Section 2.3); and (3) in many cases of human exposure (especially those involving intake from water or soil, which are of greatest concern to residents near wastes sites), the precise chemical speciation is not known.

Gallium arsenide (GaAs) is another inorganic arsenic compound of potential human health concern, due to its widespread use in the microelectronics industry. Available toxicokinetic data suggest that although gallium arsenide is poorly soluble, it undergoes slow dissolution and oxidation to form gallium trioxide and arsenite (Webb et al. 1984, 1986). Therefore, the toxic effects of this compound are expected to be attributable to the arsenite that is liberated, plus the additional effects of the gallium species.

It is beyond the scope of this profile to provide detailed toxicity data on other less common inorganic arsenic compounds (e.g., As_2S_3), but these are expected to be of approximately equal or lesser toxicity than the oxycompounds, depending mainly on solubility (see Section 2.3).

Although organic arsenicals are usually viewed as being less toxic than the inorganics, several methyl and phenyl derivatives of arsenic that are widely used in agriculture are of possible human health concern. Chief among these are monomethyl arsonic acid (MMA) and its salts, (monosodium methane arsonate [MSMA] and disodium methane arsonate [DSMA]), dimethyl arsinic acid (DMA, also known as cacodylic acid) and its sodium salt (sodium dimethyl arsinite, or sodium cacodylate), and roxarsone (3-nitro-4-hydroxyphenylarsonic acid). As with the inorganic compounds, there are toxicological differences between these various organic derivatives, but for the purposes of this profile these

differences have not been emphasized, because data are rarely adequate to permit rigorous quantitative comparisons between different chemicals, and most data are derived from studies in animals. As discussed below, animals do not appear to be good quantitative models for inorganic arsenic toxicity in humans, but it is not known if this also applies to toxicity of organic arsenicals.

Several organic arsenicals are found to accumulate in fish and shellfish. These derivatives (mainly arsenobetaine and arsenocholine, also referred to as "fish arsenic") have been studied by several researchers and have been found to be essentially nontoxic (Brown et al. 1990; Cannon et al. 1983; Charbonneau et al. 1978a; Kaise et al. 1985; Luten et al. 1982; Siewicki 1981; Tam et al. 1982; Yamauchi et al. 1986a). Thus, these compounds are not considered further here.

Arsine (AsH_3) and its methyl derivatives, although highly toxic, are also not considered in this profile, since these compounds are either gases or volatile liquids that are unlikely to be present at levels of concern at hazardous waste sites.

Use of Animal Data. An additional complexity to the analysis of arsenic toxicity is that most laboratory animals appear to be substantially less susceptible to arsenic than humans. For example, chronic oral exposure of humans to inorganic arsenic at doses of 0.05–0.1 mg/kg/day is frequently associated with neurological (Barton et al. 1992; Goddard et al. 1992; Guha Mazumder et al. 1988; Haupert et al. 1996; Hindmarsh et al. 1977; Huang et al. 1985; Sass et al. 1993; Silver and Wainman 1952; Szuler et al. 1979; Tay and Seah 1975; Valentine et al. 1981) or hematological signs of arsenic toxicity (Glazener et al. 1968; Guha Mazumder et al. 1988; Prasad and Rossi 1995; Sass et al. 1993; Tay and Seah 1975), but no characteristic neurological or hematological signs of arsenism were detected in monkeys, dogs, or rats chronically exposed to arsenate or arsenite at doses of 0.7–2.8 mg As/kg/day (Byron et al. 1967; EPA 1980f; Heywood and Sortwell 1979). This may be because the studies were not conducted for a sufficient length of time, or because too few animals were used. Moreover, while there is good evidence that arsenic is carcinogenic in humans by both oral and inhalation routes, evidence of arsenic-induced carcinogenicity in animals is mostly negative. For these reasons, quantitative dose-response data from animals are not judged to be reliable for determining levels of significant human exposure, and will be considered only briefly except when human data are lacking.

2.2.1 Inhalation Exposure

Most information on human inhalation exposure to arsenic derives from occupational settings such as smelters and chemical plants, where the predominant form of airborne arsenic is arsenic trioxide dust. One limitation to this type of study is that exposure data are usually difficult to obtain, especially from earlier time periods when exposure levels were higher than in recent years. This is further complicated by the fact that significant oral and dermal exposures are also likely to occur under these conditions and co-exposure to other metals and chemicals is also common. Thus, studies of this type are, like virtually all epidemiological studies, subject to some limitations and uncertainties. Table 2-1 and Figure 2-1 summarize studies that provide the most reliable quantitative data on health effects in humans, along with several studies in animals exposed to arsenic trioxide and other inorganic arsenic compounds by the inhalation route. Data for organic arsenicals are shown in Table 2-2 and Figure 2-2. All exposure data are expressed as milligrams of arsenic (as the element) per cubic meter of air (mg As/m^3). These studies and others that provide useful qualitative information on health effects of inorganic and organic arsenicals are discussed below.

2.2.1.1 Death

Inorganic Arsenicals. Although there are many studies of humans exposed to arsenic in air, no cases of lethality from short-term exposure were located. This suggests that death is not likely to be of concern following acute exposure, even at the very high exposure levels (1–100 mg As/m^3) found previously in the workplace (e.g., Enterline and Marsh 1982; Jarup et al. 1989; Lee-Feldstein 1986). Delayed lethality from chronic exposure attributable to increased risk of cardiovascular disease or lung cancer is discussed below in Sections 2.2.1.2 and 2.2.1.8, respectively. The only report of a lethal effect of inhaled inorganic arsenic in animals was a developmental toxicology study in which four of nine pregnant rats died, and one rat was euthanized *in extremis*, between days 12 and 19 of gestation after 30–35 days of exposure to an aerosol of arsenic trioxide at an exposure concentration of 20 mg As/m^3 (Holson et al. 1999). These animals exhibited severe hyperemia and plasma discharge into the intestinal lumen at autopsy. In this same study, there was 100% mortality in groups of 10 pregnant rats after 1 day of exposure to concentrations $100 mg/$m^3$ (76 mg As/m^3).

Organic Arsenicals. No studies were located regarding death in humans after inhalation exposure to organic arsenicals. A 2-hour LC_{50} of 2,117 mg As/m^3 was calculated for DMA in female rats (Stevens et al. 1979). This LC_{50} is shown in Table 2-2 and Figure 2-2. Male rats and mice of both sexes were less

Table 2-1. Levels of Significant Exposure to Inorganic Arsenic - Inhalation

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
ACUTE EXPOSURE							
Immunological/Lymphoreticular							
1	Mouse (CD-1)	3 hr		0.123 F	0.271 F (decr pulmonary bactericidal activity and incr susceptibility to streptococcal infection)		Aranyi et al. 1985 As(+3)
2	Mouse (CD-1)	5 d 3 hr/d		0.259 F	0.519 F (decr pulmonary bactericidal activity and incr susceptibility to streptococcal infection)		Aranyi et al. 1985 As(+3)
Developmental							
3	Mouse (CFLP)	Gd 9-12 4 hr/d		0.20	2.2 (10% decr avg fetal body wt)	21.6 (incr fetal deaths, skeletal malformations, and retarded growth)	Nagymajtenyi et al. 1985 As(+3)
INTERMEDIATE EXPOSURE							
Death							
4	Rat (CD)	14 d pre-mating thru Gd 19 7 d/wk 6 hr/d				20 F (5/10 dams died)	Holson et al. 1999 As(+3)

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

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
Systemic							
5	Rat (CD)	14 d pre-mating thru Gd 19 7 d/wk 6 hr/d	Resp	2 F	8 F (rales, dried red material around nose)		Holson et al. 1999 As(+3)
			Bd Wt	2 F	8 F (decr body wt gain during gestation)		
6	Rat (CD)	14 d pre-mating thru Gd 19 7 d/wk 6 hr/d	Resp	0.9 F	8 F (rales)	20 F (labored breathing, gasping)	Holson et al. 1999 As(+3)
			Gastro	8 F		20 F (gross gastrointestinal lesions)	
			Bd Wt	8 F		20 F (drastic decr body wt)	
Immunological/Lymphoreticular							
7	Mouse (CD-1)	4 wk 5 d/wk 3 hr/d		0.126 F	0.245 F (decr pulmonary bactericidal activity)		Aranyi et al. 1985 As(+3)
Reproductive							
8	Rat (CD)	14 d pre-mating thru Gd 19 7 d/wk 6 hr/d		8 F			Holson et al. 1999 As(+3)
9	Rat (CD)	14 d pre-mating thru Gd 19 7 d/wk 6 hr/d		20 F			Holson et al. 1999 As(+3)

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

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
Developmental							
10	Rat (CD)	14 d pre-mating thru Gd 19 7 d/wk 6 hr/d		8			Holson et al. 1999 As(+3)
11	Rat (CD)	14 d pre-mating thru Gd 19 7 d/wk 6 hr/d		8		20 (marked incr in post-implantation loss and marked decr in viable fetuses)	Holson et al. 1999 As(+3)
CHRONIC EXPOSURE							
Systemic							
12	Human	23 yr (avg)	Cardio			0.36 M (incr incidence of vasospasticity and clinical Raynaud's phenomenon)	Lagerkvist et al. 1986 As(+3)
13	Human	6-8 yr 8 hr/day	Dermal		0.007 M (dermatitis)		Mohamed 1998 As(+3)
14	Human	0.5-50 yr	Resp	0.613			Perry et al. 1948 As(+3)
			Dermal		0.078 (mild pigmentation keratosis of skin)	0.613 (gross pigmentation with hyperkeratinization of exposed areas, wart formation)	

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

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
Neurological							
15	Human	28 yr (avg)			0.31 M (decr nerve conduction velocity)		Lagerkvist and Zetterlund 1994 As(+3)
Developmental							
16	Human	NS		5.5E-5		0.0007 (incr risk of stillbirth)	Ihrig et al. 1998 As(+3)
Cancer							
17	Human	1->30 yr				0.213 M (CEL: lung cancer)	Enterline et al. 1987a As(+3)
18	Human	19.5 yr (avg)				0.069 M (CEL: lung cancer)	Enterline et al. 1987b As(+3)
19	Human	3 mo->30 yr				0.2 M (CEL: lung cancer)	Jarup and Pershagen 1991 As(+3)
20	Human	3 mo->30 yr				0.05 M (CEL: lung cancer)	Jarup et al. 1989 As(+3)
21	Human	1->30 yr				0.38 M (CEL: lung cancer)	Lee-Feldstein 1986 As(+3)

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

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL		Reference Chemical Form
					Less serious (mg/m3)	Serious (mg/m3)	
22	Human	14.8 yr (avg)				0.3 M (CEL: lung cancer)	Welch et al. 1982 As(+3)

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

avg = average; Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); decr = decreased; F = female; Gd = gestation day; hr = hour(s); incr = increased; LOAEL = lowest-observable-adverse-effect level; M = male; mo = month(s); NOAEL = no-observable-adverse-effect level; Resp = respiratory; wk = week(s); wt = weight; yr = year(s)

Figure 2-1. Levels of Significant Exposure to Inorganic Arsenic - Inhalation

Acute (≤14 days)

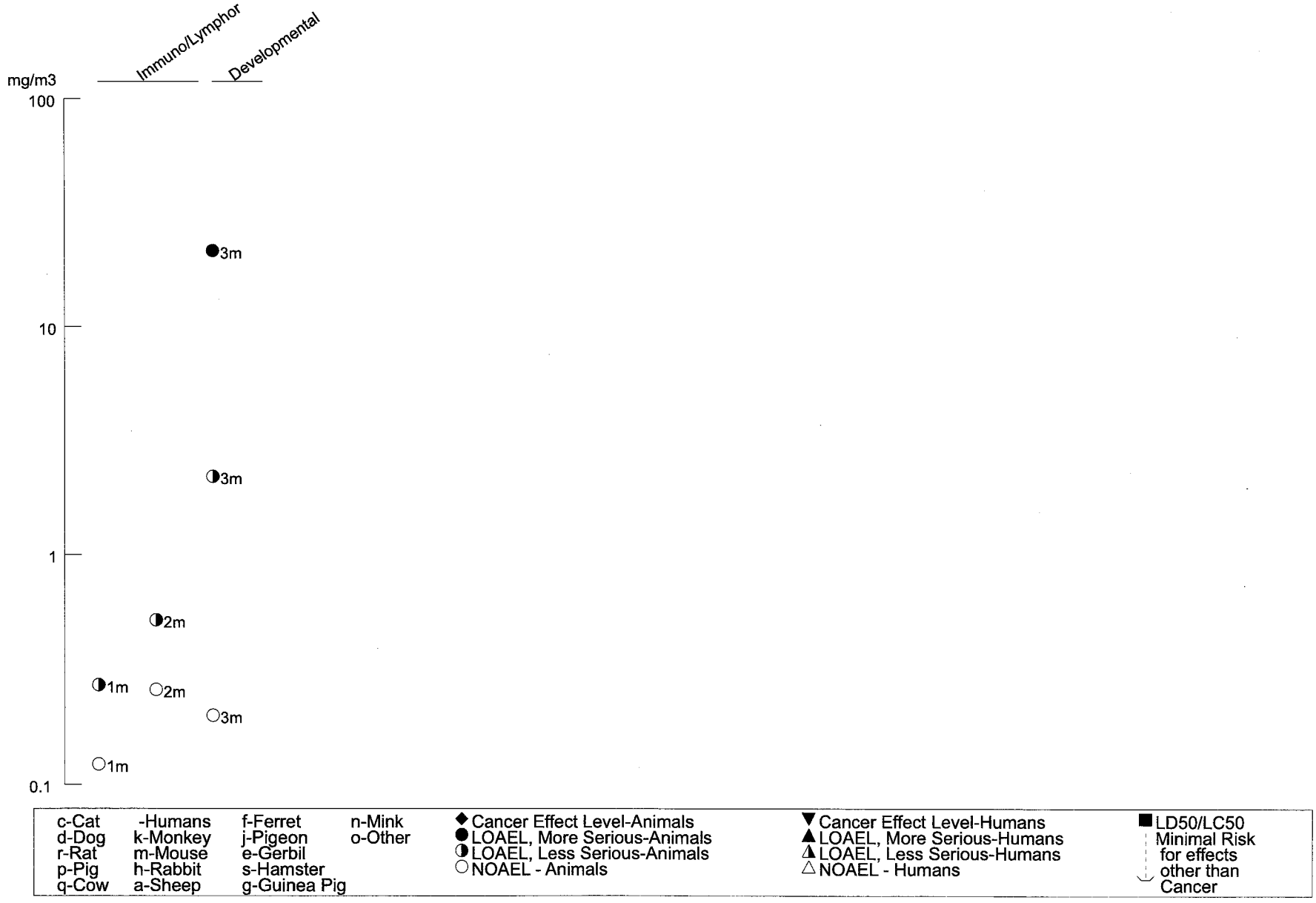
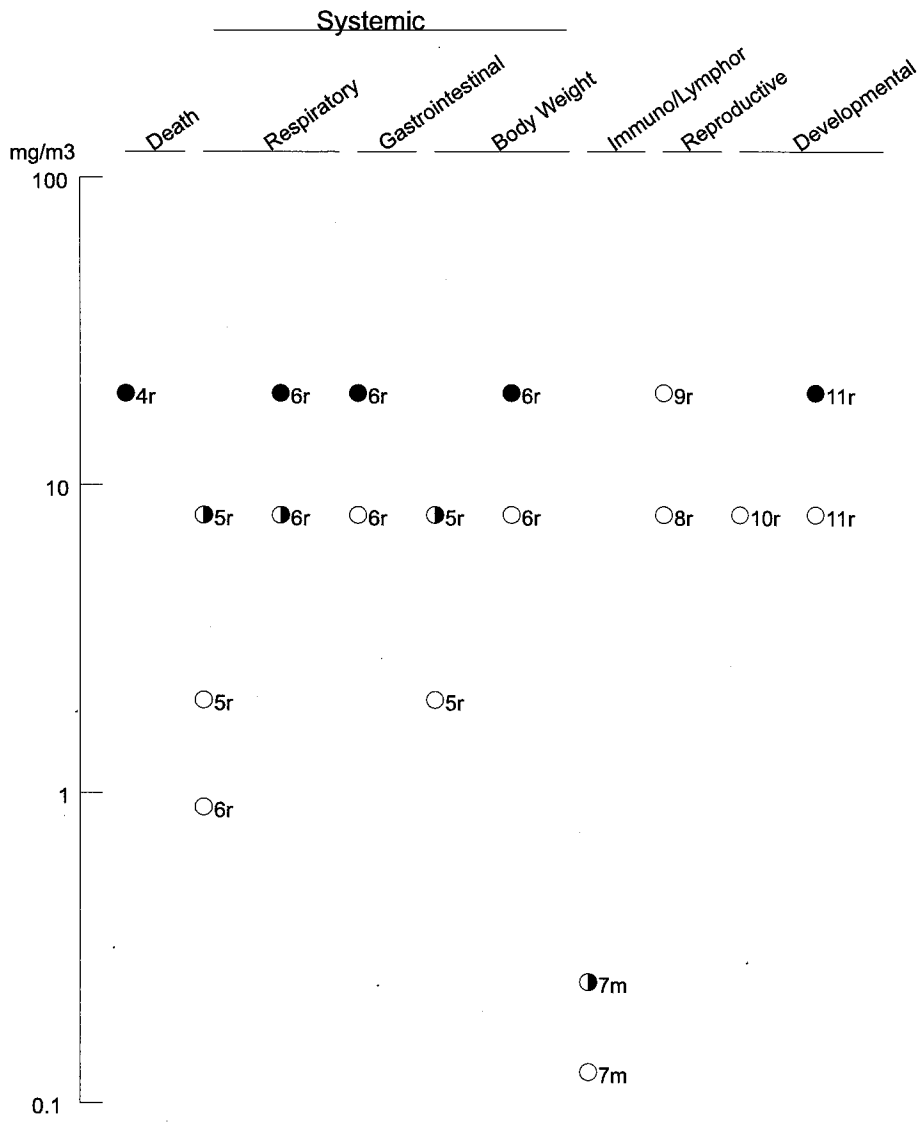


Figure 2-1. Levels of Significant Exposure to Inorganic Arsenic - Inhalation (*continued*)

Intermediate (15-364 days)



c-Cat	-Humans	f-Ferret	n-Mink	◆ Cancer Effect Level-Animals	▼ Cancer Effect Level-Humans	■ LD50/LC50
d-Dog	k-Monkey	j-Pigeon	o-Other	● LOAEL, More Serious-Animals	▲ LOAEL, More Serious-Humans	Minimal Risk for effects other than Cancer
r-Rat	m-Mouse	e-Gerbil		◑ LOAEL, Less Serious-Animals	◭ LOAEL, Less Serious-Humans	
p-Pig	h-Rabbit	s-Hamster		○ NOAEL - Animals	△ NOAEL - Humans	
q-Cow	a-Sheep	g-Guinea Pig				

Figure 2-1. Levels of Significant Exposure to Inorganic Arsenic - Inhalation (*continued*)

Chronic (≥365 days)

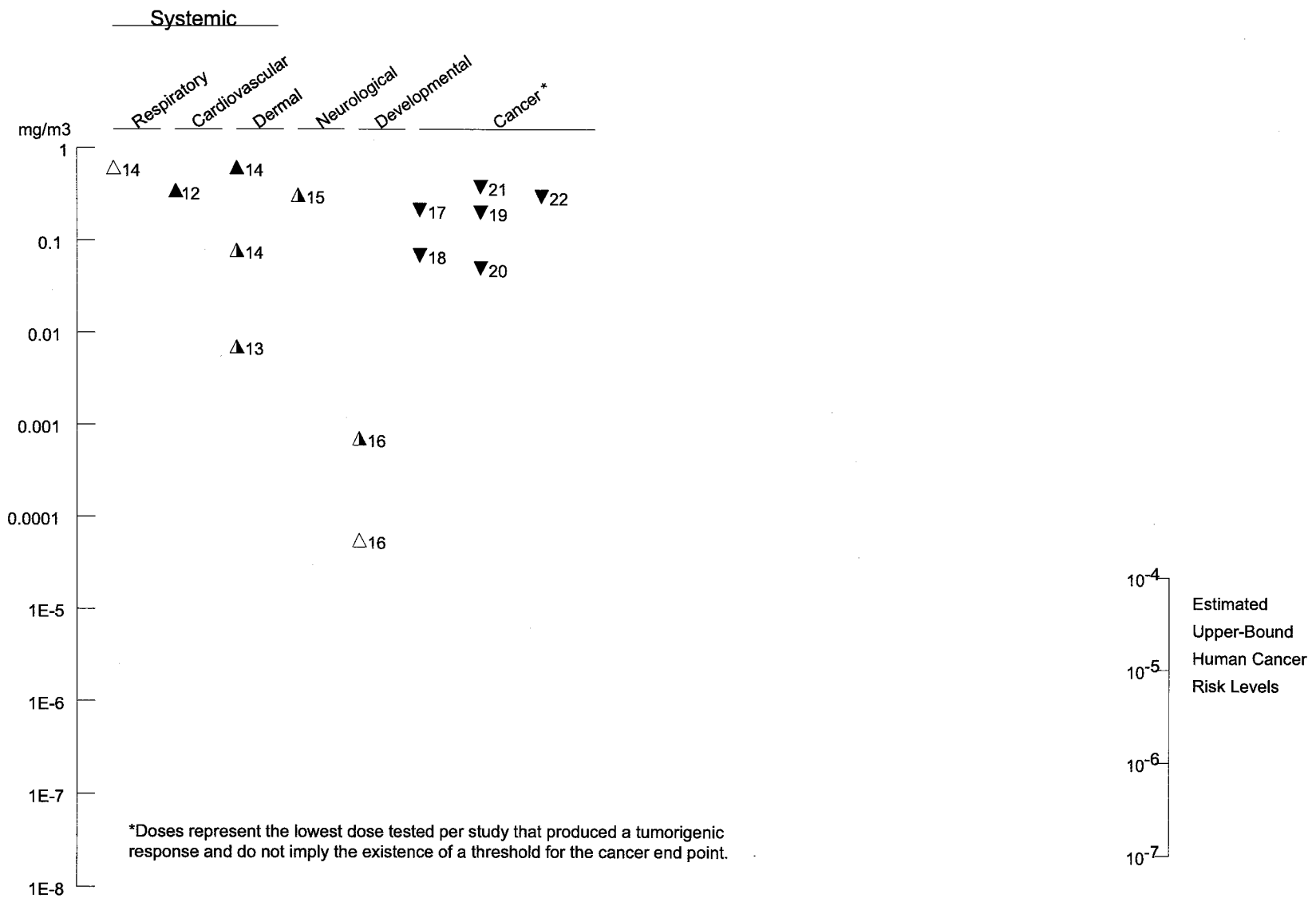


Table 2-2. Levels of Significant Exposure to Organic Arsenic - Inhalation

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
ACUTE EXPOSURE							
Death							
1	Rat (Sherman)	2 hr				2117 F (LC_{50})	Stevens et al. 1979 DMA
Systemic							
2	Rat (Sherman)	2 hr	Resp			2172 (respiratory distress)	Stevens et al. 1979 DMA
			Gastro		2172 (diarrhea)		
			Dermal	2226	3746 F (erythematous lesions of ears and feet)		
			Ocular		2172 (eye encrustation)		
			Bd Wt		2172 (unspecified decrease in body weight)		
3	Mouse (Swiss-Webster)	5 min	Resp		627 M (RD_{50})		Stevens et al. 1979 MMA
4	Mouse (Swiss-Webster)	5 min	Resp		1710 M (RD_{50})		Stevens et al. 1979 DMA

Table 2-2. Levels of Significant Exposure to Organic Arsenic - Inhalation (continued)

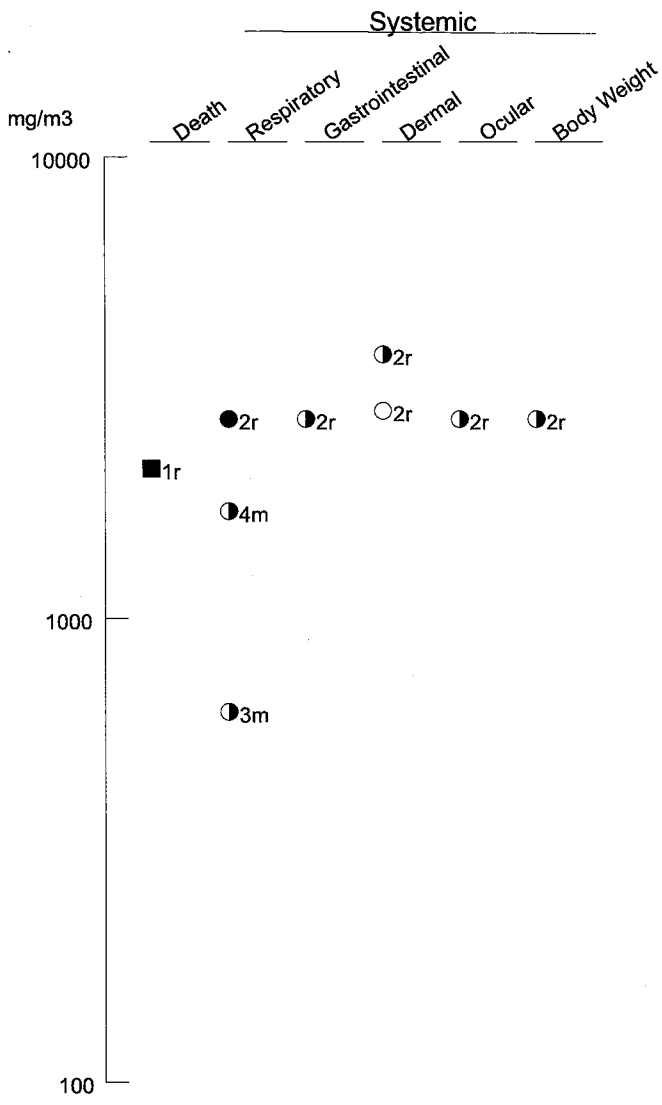
Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL		Reference Chemical Form
					Less serious (mg/m3)	Serious (mg/m3)	
CHRONIC EXPOSURE							
Systemic							
5	Human	1.45-2.12 yr (group averages)	Hemato	0.13 M			Watrous and McCaughey 1945 AA

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

AA = arsanilic acid; Bd Wt = body weight;DMA = dimethylarsinic acid; F = female; Gastro = gastrointestinal; Hemato = hematological; hr = hour(s); LC_{50} = lethal concentration, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; MMA = monomethylarsenic acid; NOAEL = no-observable-adverse-effect level; RD_{50} = concentration calculated to produce a 50% decrease in respiratory rate; Resp = respiratory; yr = year(s)

Figure 2-2. Levels of Significant Exposure to Organic Arsenic - Inhalation

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

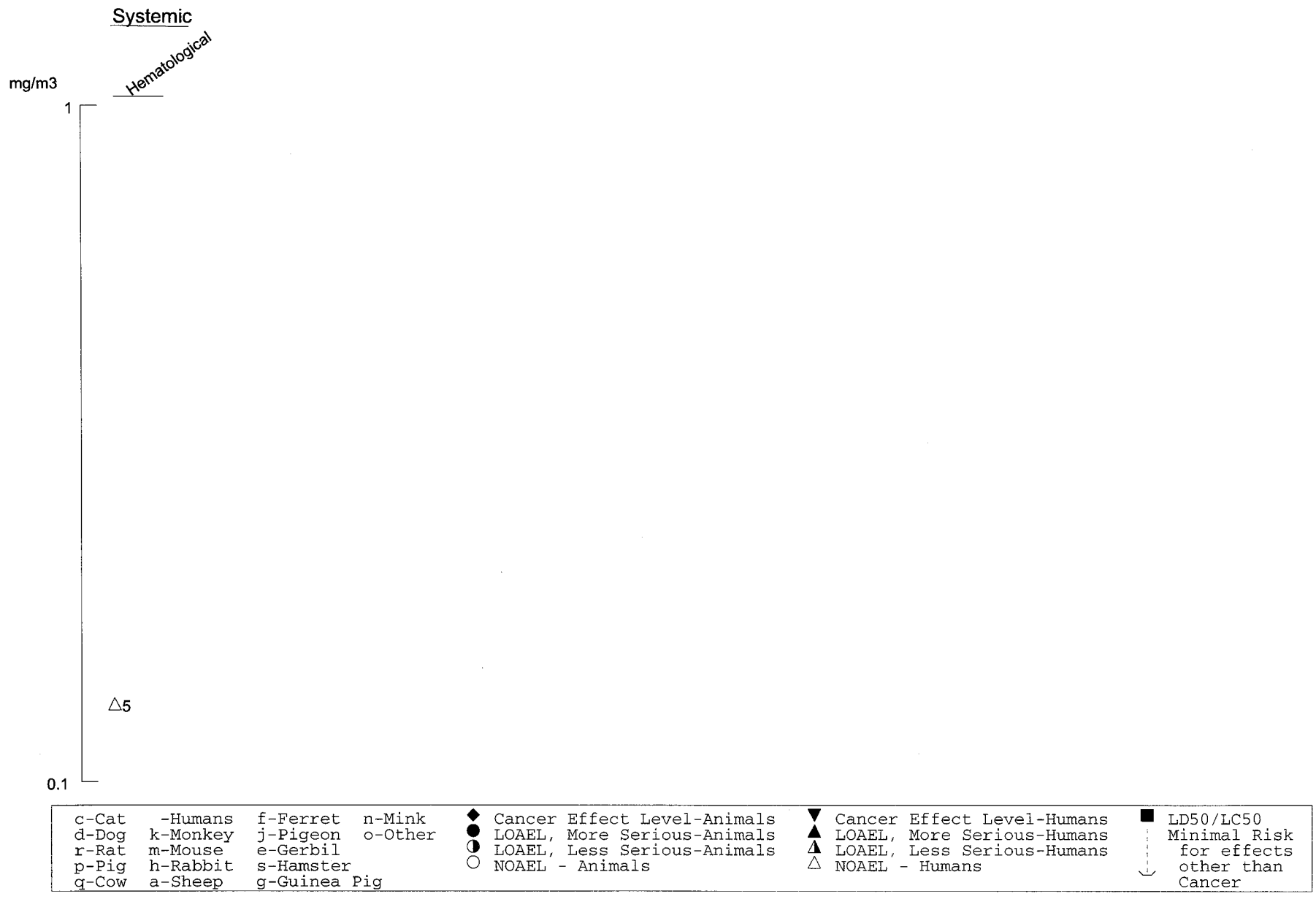
◆ Cancer Effect Level-Animals
● LOAEL, More Serious-Animals
◑ LOAEL, Less Serious-Animals
○ NOAEL - Animals

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

■ LD50/LC50
Minimal Risk for effects other than Cancer

Figure 2-2. Levels of Significant Exposure to Organic Arsenic - Inhalation (*continued*)

Chronic (≥365 days)



susceptible, with only a few deaths after 2-hour exposures as high as 3,746 mg As/m^3 in rats and 3,474 mg As/m^3 in mice (Stevens et al. 1979). The cause of death was not specified, but was probably due to lung injury (see Section 2.2.1.2). No deaths were observed among rats and mice exposed to DSMA (the disodium salt of MMA) at concentrations up to 2,485 mg As/m^3 in rats and 2,811 mg As/m^3 in mice (Stevens et al. 1979). Chamber atmospheres at these high concentrations were so dense that it was difficult to see the animals clearly. These data indicate that there is no significant risk of acute lethality from concentrations of DMA or MMA that might be encountered in the environment or the workplace.

2.2.1.2 Systemic Effects

The highest NOAEL values and all reliable LOAEL values for systemic effects from inhalation exposure to inorganic arsenicals in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1, while the corresponding data for organic arsenicals are shown in Table 2-2 and Figure 2-2.

Respiratory Effects

Inorganic Arsenicals. Workers exposed to arsenic dusts in air often experience irritation to the mucous membranes of the nose and throat. This may lead to laryngitis, bronchitis, or rhinitis (Dunlap 1921; Lundgren 1954; Morton and Caron 1989; Pinto and McGill 1953), and very high exposures (characteristic of workplace exposures in the past) can cause perforation of the nasal septum (Dunlap 1921; Pinto and McGill 1953; Sandstrom et al. 1989). Despite the known respiratory irritant effects of arsenic, there have been few systematic investigations of respiratory effects in humans exposed to arsenic. Perry et al. (1948) found no difference in chest x-rays or respiratory performance (vital capacity and exercise-tolerance tests) between unexposed and exposed workers in a cross-sectional study at a factory where sodium arsenite was prepared. The NOAEL of 0.613 mg As/m^3 for respiratory effects in this study is shown in Table 2-1 and plotted in Figure 2-1.

Increased mortality due to respiratory disease has been reported in some cohort mortality studies of arsenic-exposed workers, but no conclusive evidence of an association with arsenic has been produced. In studies of workers exposed to arsenic trioxide at the Anaconda copper smelter in Montana, mortality due to noncancer respiratory disease (e.g., emphysema) was significantly increased compared to the general population (Lee-Feldstein 1983; Welch et al. 1982). However, the data were not adjusted for smoking (a well-known confounder for respiratory disease), and analysis of the data with respect to

arsenic exposure level did not show a clear dose-response. Similarly, Enterline et al. (1995) found a significant excess of non-malignant respiratory disease mortality in workers at the ASARCO copper smelter in Tacoma, Washington, but only a slight negative relation to cumulative arsenic exposure. Xuan et al. (1993) found an increase in the relative risk of mortality from pneumoconiosis associated with arsenic exposure in a cohort of tin miners in China. However, this finding was based on a small number of observations (n=32), a clear exposure-response relationship with arsenic was not established, and the miners experienced confounding exposures to dust (a known risk factor for pneumoconiosis) and to radon. These studies were all considered to be inconclusive as to the relationship between inhaled inorganic arsenic and respiratory disease.

Respiratory symptoms were observed in a study of developmental effects in rats. Pregnant female rats exposed to arsenic trixode dust starting 14 days prior to mating and continuing through mating and gestation exhibited rales at 8 mg As/m^3 and labored breathing and gasping at 20 mg As/m^3, with no symptoms at 2 mg As/m^3 (Holson et al. 1999). The lungs were examined by gross necropsy and no lesions were found. Intratracheal instillation of arsenic trioxide (13 mg As/kg) or gallium arsenide (1.5–52 mg As/kg) can cause marked irritation and hyperplasia in the lungs of rats and hamsters (Goering et al. 1988; Ohyama et al. 1988; Webb et al. 1986, 1987). Since this sort of response is produced by a number of respirable particulate materials, it is likely that the inflammatory response is not specifically due to the arsenic.

Organic Arsenicals. No studies were located regarding respiratory effects in humans exposed to organic arsenicals. Short-term exposure of rats and mice to high concentrations (2,172 mg As/m^3 or greater) of DMA caused respiratory distress, and necropsy of animals that died revealed bright red lungs with dark spots (Stevens et al. 1979). Respiratory distress was also observed in rats and mice exposed to high levels (2,485 mg As/m^3 or greater) of the disodium salt of MMA (Stevens et al. 1979), although none of the MMA-exposed animals died. Respiratory distress appears to be associated with inhalation of very high concentrations of organic arsenicals. In 5-minute whole-body plethysmography trials, DMA and the disodium salt of MMA had RD_{50} (concentration calculated to produce a 50% decrease in respiration rate) values of 1,710 and 627 mg As/m^3, respectively (Stevens et al. 1979). Based on these RD_{50} values, neither DMA nor MMA is considered to be a potent respiratory irritant. Reliable LOAELs for respiratory effects of organic arsenic are shown in Table 2-2 and Figure 2-2.

Cardiovascular Effects

Inorganic Arsenicals. There is some evidence from epidemiological studies that inhaled inorganic arsenic can produce effects on the cardiovascular system. Cardiovascular effects following oral exposure to arsenic are well known (see Section 2.2.2.2). A cross-sectional study of workers exposed to an estimated time-weighted average of 0.36 mg As/m^3 (as arsenic trioxide) at the Ronnskar copper smelter in Sweden for an average of 23 years showed that smelter workers had significantly increased incidences of Raynaud's phenomenon (a peripheral vascular disease characterized by spasm of the digital arteries and numbness of the fingers) and showed increased vasospasticity (constriction of blood vessels) in response to cold when tested in the fingers (Lagerkvist et al. 1986). A follow-up study conducted 2–3 years later found that vasospasticity measurements in exposed workers had improved concurrent with a reduction in arsenic exposure levels, although symptoms of peripheral vascular effects (cold hands or feet, white fingers, numbness in fingers or feet) were still common (Lagerkvist et al. 1988). A cross-sectional study including 46 workers in Denmark with varying, unquantified occupational exposure to arsenic in different occupations found that systolic blood pressure was significantly increased in the arsenic workers (median=125 mmHg) compared with controls (median=117 mmHg) (Jensen and Hansen 1998). Diastolic pressure was also increased in this study (77.9 vs. 74.7 mmHg), although the difference from controls was not statistically significant.

Cohort mortality studies of arsenic-exposed workers at the ASARCO copper smelter in Tacoma, Washington (Enterline et al. 1995), Anaconda copper smelter in Montana (Lee-Feldstein 1983; Welch et al. 1982), Ronnskar copper smelter in Sweden (Wall 1980), orchard workers in Washington state (Tollestrup et al. 1995), and tin miners in China (Qiao et al. 1997; Xuan et al. 1993) have all reported increased risk of mortality from cardiovascular disease, specifically ischemic heart disease and cerebrovascular disease, in the cohorts studied. However, none of these studies provided conclusive evidence that the observed increase in risk was due to arsenic exposure. The studies in the ASARCO and Anaconda copper smelter workers failed to find a clear dose-response relationship with arsenic (Enterline et al. 1995; Welch et al. 1982), while a follow-up study of the Ronnskar smelter workers not only found lack of a dose-response, but also that the risk of cardiovascular disease was no longer elevated in the cohort (Jarup et al. 1989). The studies in orchard workers and tin miners were limited by confounding exposures to copper, lead, and radon, respectively (Qiao et al. 1997; Tollestrup et al. 1995). The risk of cardiovascular disease mortality in the tin miners not only showed no dose-response relationship with arsenic exposure, but was positively associated with radon exposure, suggesting that radon may have been responsible for the increased cardiovascular risk in this cohort (Xuan et al. 1993).

The LOAEL for Raynaud's phenomenon and vasospasticity identified by Lagerkvist et al. (1986) is shown in Table 2-1 and Figure 2-1. No studies were located regarding cardiovascular effects in animals after inhalation exposure to inorganic arsenic.

Organic Arsenicals. No studies were located regarding cardiovascular effects in humans or animals after inhalation exposure to organic arsenicals.

Gastrointestinal Effects

Inorganic Arsenicals. Several case studies have reported nausea, vomiting, and diarrhea in workers with acute arsenic poisoning following occupational inhalation exposure (Beckett et al. 1986; Bolla-Wilson and Bleecker 1987; Ide and Bullough 1988; Morton and Caron 1989; Pinto and McGill 1953). Although gastrointestinal effects are not typically associated with arsenic poisoning by inhalation (Pinto and McGill 1953), such effects are a common feature of oral ingestion of high doses of arsenic (see Section 2.2.2.2), and it is possible that mucociliary transport of arsenic dust from the lungs to the gut could be responsible for the effects in these cases. Exposure levels were not reliably estimated for any of these cases.

The only report of gastrointestinal effects of inhaled inorganic arsenic in animals was a developmental toxicology study in which four of nine pregnant rats died, and one rat was euthanized *in extremis*, between days 12 and 19 of gestation after 30–35 days of exposure to an aerosol of arsenic trioxide at an exposure concentration of 20 mg As/m^3 (Holson et al. 1999). These animals exhibited severe hyperemia and plasma discharge into the intestinal lumen at autopsy. Exposure to 8 mg As/m^3 did not produce gross gastrointestinal lesions.

Organic Arsenicals. Data regarding gastrointestinal effects in people exposed to organic arsenic in the air are limited. The frequency of gastrointestinal complaints was no higher than controls in workers exposed to arsanilic acid (i.e., 4-aminophenyl arsonic acid) at mean concentrations up to 0.13 mg As/m^3 in a chemical factory (Watrous and McCaughey 1945). However, this sort of data might easily be biased by workers who chose not to complain about minor symptoms, so no conclusion can be reached. Rats and mice exposed to very high levels (above 2,000 mg As/m^3) of MMA (disodium salt) or DMA experienced diarrhea (Stevens et al. 1979). The LOAEL for this effect is shown in Table 2-2 and Figure 2-2. The diarrhea could be due to transport of inhaled particulate material from the lungs to the gastrointestinal system or to direct ingestion of the compound (e.g., from grooming of the fur).

Hematological Effects

Inorganic Arsenicals. Although anemia is a common feature of arsenic poisoning following oral exposure in humans (see Section 2.2.2.2), case studies of workers with arsenic poisoning from occupational inhalation exposure reported no effects on red blood cell count (Beckett et al. 1986; Bolla-Wilson and Bleecker 1987; Ide and Bullough 1988; Morton and Caron 1989). The reason for this apparent route specificity is not clear, but might simply be related to dose. No studies were located regarding hematological effects in animals after inhalation exposure to inorganic arsenicals.

Organic Arsenicals. No effect on levels of hemoglobin, red cells, or white cells was detected in the blood of manufacturing workers (323 counts in 35 workers) exposed to airborne arsanilic acid dusts at a mean concentration of 0.13 mg As/m^3 in the workplace (Watrous and McCaughey 1945). Controls were an unspecified number of unexposed manufacturing workers with 221 complete blood counts. The NOAEL from this study is shown in Table 2-2 and Figure 2-2. No studies were located regarding hematological effects in animals after inhalation exposure to organic arsenicals.

Musculoskeletal Effects

Inorganic Arsenicals. Few data were located regarding musculoskeletal effects associated with inhalation exposure to inorganic arsenic, and none to suggest the existence of any such effects. Electromyographic examination of the calves and feet showed no differences between control and arsenic-exposed workers in a cross-sectional study of workers at the Ronnskar copper smelter in Sweden (Blom et al. 1985). No studies were located regarding musculoskeletal effects in animals after inhalation exposure to inorganic arsenicals.

Organic Arsenicals. No studies were located regarding musculoskeletal effects in humans or animals after inhalation exposure to organic arsenicals.

Hepatic Effects

Inorganic Arsenicals. There is no evidence that inhaled inorganic arsenic produces effects on the liver, although few data are available. Case studies of workers with inhalation arsenic poisoning that included liver function tests did not find any evidence of hepatic dysfunction (Bolla-Wilson and Bleecker 1987;

Ide and Bullough 1988). No studies were located regarding hepatic effects in animals after inhalation exposure to inorganic arsenicals.

Organic Arsenicals. No studies were located regarding hepatic effects in humans or animals after inhalation exposure to organic arsenicals.

Renal Effects

Inorganic Arsenicals. The limited data available do not suggest any relationship between inhalation of inorganic arsenic and kidney effects. A cross-sectional study of renal function parameters in glass factory workers exposed to arsenic (concentrations unknown) found no meaningful differences from controls in urinary levels of several proteins (albumin, retinol binding protein, β_2-microglobulin, brush-border antigen) used as markers of glomerular damage or tubular cell exfoliation (Foa et al. 1987). Routine clinical urinalysis was normal when included in case studies of workers with inhalation arsenic poisoning (Ide and Bullough 1988; Morton and Caron 1989). No studies were located regarding renal effects in animals after inhalation exposure to inorganic arsenicals.

Organic Arsenicals. No studies were located regarding renal effects in humans or animals after inhalation exposure to organic arsenicals.

Dermal Effects

Inorganic Arsenicals. Dermatitis has frequently been observed in industrial workers exposed to inorganic arsenic in the air, with the highest rates occurring in the workers with the greatest arsenic exposure (Dunlap 1921; Holmqvist 1951; Lagerkvist et al. 1986; Pinto and McGill 1953). Limited quantitative information is available regarding the exposure levels that produce dermatitis. A cross-sectional study of workers at a factory where sodium arsenite was prepared found that workers with the highest arsenic exposure (mean air levels ranging from 0.384 to 1.034 mg As/m^3 and estimated to average 0.613 mg As/m^3) tended to be grossly pigmented with hyperkeratinization of exposed skin and to have multiple warts (Perry et al. 1948). In the same study, workers with lower arsenic exposure (estimated to average 0.078 mg As/m^3) were much less affected, but still had a higher incidence of pigmentation keratosis than controls. Dermatitis characterized by hyperpigmentation, folliculitis, and superficial ulcerations was observed in 11 employees in one department of a Malaysian tin smelter (total of 500 employees in the plant) exposed to mean arsenic oxide concentrations ranging from 0.005 to

0.014 mg As_2O_3/m^3 (estimated average exposure=0.007 mg As/m^3) (Mohamed 1998). LOAEL values identified by Perry et al. (1948) and Mohamed (1998) are shown in Table 2-1 and Figure 2-1. NOAEL values for dermal irritation have not been identified. Dermal effects (hyperkeratoses, hyperpigmentation) are also very common in people exposed to inorganic arsenic by the oral route (see Section 2.2.2.2). No studies were located on dermal effects in animals after inhalation exposure to inorganic arsenicals.

Organic Arsenicals. Data regarding dermal effects in people exposed to organic arsenic in the air are limited. Complaints of keratosis were roughly two-fold higher than unexposed controls in female packaging workers exposed to arsanilic acid at an average concentration of 0.05 mg As/m^3 and in male manufacturing workers exposed to an average concentration of 0.13 mg As/m^3 in a chemical factory (Watrous and McCaughey 1945). This observation is consistent with the arsenic database as a whole, but limitations in study methodology (e.g., alternate sources of effects were not investigated, workers might choose not to report minor complaints to company officials) make the reliability of this observation uncertain. Female rats exposed to DMA at 3,746 mg As/m^3 developed erythematous lesions on the feet and ears (Stevens et al. 1979); these lesions did not develop in females exposed at lower concentrations (2,226 mg As/m^3) or males. The NOAEL and LOAEL values for dermal effects in female rats are shown in Table 2-2 and Figure 2-2. It seems likely these effects were due to direct irritation from dermal contact with the dust.

Ocular Effects

Inorganic Arsenicals. Chemical conjunctivitis, characterized by redness, swelling, and pain, has been observed in workers exposed to arsenic dusts in air, usually in combination with facial dermatitis (Dunlap 1921; Pinto and McGill 1953). No information was located regarding air levels of arsenic that produce this effect. No studies were located on ocular effects in animals after inhalation exposure to inorganic arsenicals.

Organic Arsenicals. No studies were located on ocular effects in humans after inhalation exposure to organic arsenicals. Rats and mice exposed to high concentrations of DMA ($2,172 mg As/m^3) developed an encrustation around the eyes (Stevens et al. 1979). This LOAEL is shown in Table 2-2 and Figure 2-2. It seems likely that these effects were due to direct irritation from ocular contact with the dust.

Body Weight Effects

Inorganic Arsenicals. No studies were located on body weight effects in humans after inhalation exposure to inorganic arsenicals. Female rats exposed to arsenic trioxide dust starting 14 days before mating and continuing through mating and gestation showed a marked decrease in body weight and food consumption at 20 mg As/m^3 (preliminary study) and a smaller decrease at 8 mg As/m^3 (definitive study), with no effect at 2 mg As/m^3 (Holson et al. 1999).

Organic Arsenicals. No studies were located on body weight effects in humans after inhalation exposure to organic arsenicals. Rats and mice exposed to high concentrations of DMA ($2,172 mg As/$m^3$) for 2 hours had an unspecified decrease in body weight gain during the subsequent 14 days (Stevens et al. 1979). This LOAEL is shown in Table 2-2 and Figure 2-2.

2.2.1.3 Immunological and Lymphoreticular Effects

Inorganic Arsenicals. A single study was located regarding the immunological and lymphoreticular effects of inhaled inorganic arsenic in humans. Bencko et al. (1988) detected no abnormalities in serum levels of immunoglobins in workers exposed to arsenic in a coal-burning power plant. However, the levels of arsenic were not measured and may have been too low for this to be a meaningful result. The immune effects of inhaled arsenic in animals were studied by Aranyi et al. (1985). Female mice exposed to arsenic trioxide aerosol for 3 hours showed a concentration-related decrease in pulmonary bactericidal activity (presumably as a result of injury to alveolar macrophages) and a corresponding concentration-related increase in susceptibility to introduced respiratory bacterial pathogens. Similar results were found when the exposure was repeated over 1- and 4-week periods. The NOAEL and LOAEL values for this study are shown in Table 2-1 and Figure 2-1.

Intratracheal studies in animals offer some support for an immune effect of inhaled inorganic arsenic. Decreases in humoral response to antigens and in several complement proteins were noted in mice given an intratracheal dose of 5.7 mg As/kg as sodium arsenite (Sikorski et al. 1989), although these changes were not accompanied by any decrease in resistance to bacterial or tumor cell challenges. Animals given an intratracheal dose of GaAs (25 mg As/kg or higher) also displayed a variety of changes in numerous immunological end points (some increased, some decreased) (Burns and Munson 1993; Sikorski et al. 1989). Whether these effects were due to a direct effect on the immune system or were secondary to the inflammatory effect of GaAs on the lung (see Section 2.2.1.2, above) is uncertain.

Organic Arsenicals. No studies were located regarding immunological and lymphoreticular effects in humans or animals after inhalation exposure to organic arsenicals.

2.2.1.4 Neurological Effects

Inorganic Arsenicals. There is evidence from epidemiological studies that inhaled inorganic arsenic can produce neurological effects. Cross-sectional studies of copper smelter workers at the ASARCO smelter in Tacoma, Washington (Feldman et al. 1979) and the Ronnskar smelter in Sweden (Blom et al. 1985; Lagerkvist and Zetterlund 1994) have demonstrated peripheral neurological effects in workers associated with arsenic trioxide exposure. At the ASARCO smelter, the prevalence of clinically diagnosed peripheral neuropathy was markedly higher in arsenic-exposed workers (26/61=43%) than controls (4/33=12%), and although the difference in mean nerve conduction velocities (NCV) was not statistically significant, mean peroneal motor NCV was lower in arsenic-exposed workers than controls and all 12 cases of abnormally low NCV occurred in the arsenic group (Feldman et al. 1979). Similar results were observed at the Ronnskar smelter, where Blom et al. (1985) reported significantly increased prevalence of workers with abnormally low NCV in the exposed group, and lower, but not statistically significant, mean NCV in five peripheral nerves. A follow-up study on the Ronnskar workers 5 years later found that the prevalence of abnormally low NCV remained significantly increased in the exposed workers, but that the decrease in mean NCV was now also statistically significant in the tibial (motor) and sural (sensory) nerves (Lagerkvist and Zetterlund 1994). Blood lead was monitored in this study as a potential confounder, but levels were low and not considered likely by the researchers to have had any influence on the results. The follow-up Ronnskar study provided enough information to estimate that mean arsenic exposure was 0.31 mg As/m^3 and lasted an average of 28 years in the exposed group, and this LOAEL is shown in Table 2-1 and Figure 2-1.

The literature also contains several case studies of workers with inhalation arsenic poisoning who developed neurological symptoms. Although these studies do not provide reliable information on exposure levels or conclusive evidence that the observed effects were related to arsenic, the findings are suggestive. Symptoms in these cases included not only indicators of peripheral neuropathy (numbness, loss of reflexes, muscle weakness, tremors) (Ide and Bullough 1988; Morton and Caron 1989), but also frank encephalopathy (hallucinations, agitation, emotional lability, memory loss) (Beckett et al. 1986; Bolla-Wilson and Bleecker 1987; Morton and Caron 1989). Both peripheral neuropathy and encephalopathy are associated with oral exposure to inorganic arsenic (see Section 2.2.2.4).

No studies were located regarding neurological effects in animals after inhalation exposure to inorganic arsenicals. Mice given a single intratracheal dose of 200 mg/kg of GaAs displayed a decrease in overall activity 6–8 hours later, but no additional neurological evaluations were conducted on these animals (Burns and Munson 1993).

Organic Arsenicals. Data regarding neurological effects in people exposed to organic arsenic in the air are limited to a single study. The frequency of central nervous system complaints was no higher than controls in workers at a chemical factory exposed to arsanilic acid at mean concentrations up to 0.13 mg As/m^3 (Watrous and McCaughey 1945). Although peripheral nerve complaints were higher in arsenic packaging workers (mean exposure=0.05 mg As/m^3) than in unexposed controls, this was not the case in manufacturing workers with higher arsenic exposure (mean=0.13 mg As/m^3). This suggests that the effects on the peripheral nerves in the exposed packaging workers were not due to arsenic. The reliability of these data is limited by shortcomings in the study methodology (e.g., the data might easily be biased by workers who chose not to complain about minor symptoms). No studies were located regarding neurological effects in animals after inhalation exposure to organic arsenicals.

2.2.1.5 Reproductive Effects

Inorganic Arsenicals. No studies were located regarding reproductive effects in humans after inhalation exposure to inorganic arsenicals. Reproductive performance was evaluated in female rats exposed to 0.08–20 mg As/m^3 (preliminary study) or 0.2–8 mg As/m^3 (definitive study) as As_2O_3 6 hours daily from 14 days prior to mating through gestation day 19 (Holson et al. 1999). No changes occurred in the precoital interval (time to mating), mating index (percentage of rats mated), or fertility index (percentage of matings resulting in pregnancy). The NOAEL values for this study are shown in Table 2-1 and Figure 2-1.

Organic Arsenicals. No studies were located regarding reproductive effects in humans or animals after inhalation exposure to organic arsenicals.

2.2.1.6 Developmental Effects

Inorganic Arsenicals. Developmental effects associated with occupational and environmental exposure to airborne arsenic have been investigated in a series of studies at the Ronnskar copper smelter in northern Sweden (Nordstrom et al. 1978a, 1978b, 1979a, 1979b). In comparison to a northern Swedish reference

population, female employees of the smelter had a significantly increased incidence of spontaneous abortion (Nordstrom et al. 1979a), and their children had a significantly increased incidence of congenital malformations (Nordstrom et al. 1979b) and significantly decreased average birth weight (Nordstrom et al. 1978a). Increased incidence of spontaneous abortion and decreased average birth weight of children were also found in populations living in close proximity to the smelter (Nordstrom et al. 1978a, 1978b, 1979b). While these data are suggestive of developmental effects associated with occupational and environmental exposure from the smelter, the reported effects are not large, the analyses include only limited consideration of potential confounders (e.g., smoking), and there are no data relating the apparent effects specifically to arsenic exposure.

More recently, Ihrig et al. (1998) conducted a case-control study of stillbirths in the vicinity of a Texas arsenic pesticide factory that included estimation of environmental arsenic exposures using atmospheric dispersion modeling and multiple regression analysis featuring arsenic exposure, race/ethnicity, maternal age, median income, and parity as explanatory variables. There was a statistically significant increase in the risk of stillbirth in the highest exposure category (>100 ng As/m^3, midpoint=682 ng/m^3). Further analysis showed that this increase in risk was limited to people of Hispanic descent, who the researchers speculated may be an especially sensitive population due to a genetic impairment in folate metabolism. Interpretation of this study is limited by small numbers of cases and controls in the high exposure group, lack of data on smoking, potential confounding exposures to other chemicals from the factory, and failure to take into account previous years of deposition in the exposure estimates.

Arsenic has been shown to produce developmental effects by inhalation exposure in laboratory animals, although it is unclear whether or not the effects occur only at maternally toxic doses. Mice exposed to 22 mg As/m^3 (as As_2O_3) for 4 hours on days 9–12 of gestation had serious developmental effects (significant increases in the percentage of dead fetuses, skeletal malformations, and the number of fetuses with retarded growth), while those exposed to 2.2 mg As/m^3 had only a 10% decrease in average fetal body weight, and those exposed to 0.20 mg As/m^3 had no effects (Nagymajtenyi et al. 1985). The study was limited by failure to quantify malformations on a litter basis, discuss the nature and severity of the observed malformations, or report on the occurrence of maternal effects. No increases in fetal resorptions, fetal mortality, or malformations, and no decreases in fetal birth weight occurred when rats were exposed to 0.2–8 mg As/m^3 (as As_2O_3), 6 hours daily from 14 days prior to mating through gestation day 19 (Holson et al. 1999). At the 8 mg/m^3 exposure level, toxicity was observed in the dams, including rales, a dried red exudate at the nose, and lower gains in net body weight than controls. In a preliminary dose-range study, there was a marked significant increase in post-implantation loss (primarily early

resorptions) and consequent marked significant decrease in viable fetuses per litter at 20 mg As/m^3, a concentration that also produced severe maternal effects including mortality (Holson et al. 1999).

The NOAEL and LOAEL values for increased risk of stillbirth in humans identified by Ihrig et al. (1998) and those for developmental effects in rodents found by Nagymajtenyi et al. (1985) and Holson et al. (1999) are shown in Table 2-1 and Figure 2-1.

Organic Arsenicals. No studies were located regarding developmental effects in humans or animals after inhalation exposure to organic arsenicals.

2.2.1.7 Genotoxic Effects

Inorganic Arsenicals. Human and animal data are available indicating that inhaled inorganic arsenic is clastogenic. Workers exposed to unspecified concentrations of arsenic trioxide at the Ronnskar copper smelter in Sweden were found to have a significant increase in the frequency of chromosomal aberrations in peripheral lymphocytes (Beckman et al. 1977; Nordenson et al. 1978). This result is supported by an animal study that found increased chromosomal aberrations in the livers of fetuses from pregnant mice exposed to 22, but not 2.2 or 0.20, mg As/m^3 as arsenic trioxide on days 9–12 of gestation (Nagymajtenyi et al. 1985). Other genotoxicity studies on inorganic arsenicals are discussed in Section 2.5.

Organic Arsenicals. No studies were located regarding genotoxic effects in humans or animals after inhalation exposure to organic arsenicals. Other genotoxicity studies on organic arsenicals are discussed in Section 2.5.

2.2.1.8 Cancer

Inorganic Arsenicals. There is convincing evidence from a large number of epidemiological studies that inhalation exposure to inorganic arsenic increases the risk of lung cancer. Most studies involved workers exposed primarily to arsenic trioxide dust in air at copper smelters (Axelson et al. 1978; Brown and Chu 1983a, 1983b, 1983c; Enterline and Marsh 1982; Enterline et al. 1987a, 1987b, 1995; Ferreccio et al. 1996; Higgins et al. 1982; Jarup and Pershagen 1991; Jarup et al. 1989; Lee and Fraumeni 1969; Lee-Feldstein 1983, 1986; Mazumdar et al. 1989; Pinto et al. 1977, 1978; Sandstrom et al. 1989; Wall 1980; Welch et al. 1982) and mines (Liu and Chen 1996; Qiao et al. 1997; Taylor et al. 1989; Xuan et al. 1993), but increased incidence of lung cancer has also been observed at chemical plants where exposure

was primarily to arsenate (Bulbulyan et al. 1996; Mabuchi et al. 1979; Ott et al. 1974; Sobel et al. 1988). In addition, several studies suggest that residents living near smelters or arsenical chemical plants may also have increased risk of lung cancer (Brown et al. 1984; Cordier et al. 1983; Matanoski et al. 1981; Pershagen 1985), although the increases are small and are not clearly detectable in all cases (e.g., Frost et al. 1987). The strongest evidence that arsenic is responsible for the observed lung cancer comes from quantitative dose-response data relating specific arsenic exposure levels to lung cancer risk. These data are available for arsenic-exposed workers at the ASARCO copper smelter in Tacoma, Washington (Enterline and Marsh 1982; Enterline et al. 1987a, 1995; Mazumdar et al. 1989), the Anaconda copper smelter in Montana (Lee-Feldstein 1986; Welch et al. 1982), eight other U.S. copper smelters (Enterline et al. 1987b), and the Ronnskar copper smelter in Sweden (Jarup and Pershagen 1991; Jarup et al. 1989).

Enterline and Marsh (1982) reported a significant increase in respiratory cancer mortality (standard mortality ratio [SMR]=189.4) based on 104 observed respiratory cancer deaths and only 54.9 expected over the years 1941–1976 in a cohort of 2,802 male workers employed for $1 year between 1940 and 1964 at the ASARCO smelter. When the cohort was separated into low and high arsenic exposure groups, with mean estimated time-weighted average arsenic exposures of 0.054 and 0.157 mg As/m^3, respectively (based on work history, historical urinary arsenic measurements, and an experimentally derived relationship between urinary and inhaled arsenic), respiratory cancer mortality was significantly increased in both groups in a concentration-related fashion (SMR=227.7 and 291.4 in the low and high groups, respectively). Enterline et al. (1987a) re-analyzed these data using improved exposure estimates that incorporated historical measurements of arsenic in the ambient air and personal breathing zone of workers. Respiratory cancer mortality was significantly increased in a concentration-related fashion in the low (SMR=213.0), medium (SMR=312.1), and high (SMR=340.9) arsenic exposure groups, which had mean estimated time-weighted average arsenic exposures of 0.213, 0.564, and 1.487 mg As/m^3, respectively. An alternative analysis of these data by Mazumdar et al. (1989) produced similar results. Enterline et al. (1995) extended the mortality follow-up from 1976 to 1986, but reported findings similar to the earlier study in a less thorough analysis. The CEL from Enterline et al. (1987a), the most complete analysis of the ASARCO cohort with the best exposure estimates, is presented in Table 2-1 and Figure 2-1.

Respiratory cancer mortality was significantly increased (SMR=285) based on 302 observed respiratory deaths between 1938 and 1977 in a cohort of 8,045 white male workers employed for at least 1 year between 1938 and 1956 at the Anaconda smelter (Lee-Feldstein 1986). When workers were categorized according to cumulative arsenic exposure and date of hire, lung cancer mortality was significantly

increased in all groups hired between 1925 and 1947. Workers in the lowest cumulative exposure group (<10 mg-mo/m^3) were reported to have had less than 2 years exposure at an average arsenic concentration of 0.38 mg/m^3. An alternative analysis of a subset of the Anaconda cohort (n=1,800, including all 277 employees with heavy arsenic exposure and 20% of the others) that included information on smoking and other occupational exposures was performed by Welch et al. (1982). This analysis showed that lung cancer mortality increased with increasing time-weighted average arsenic exposure, with a small nonsignificant increase in the low group (SMR=138) exposed to 0.05 mg/m^3 and significant increases in the medium (SMR=303), high (SMR=375), and very high (SMR=704) groups exposed to 0.3, 2.75, and 5.0 mg/m^3, respectively. Cohort members were more likely to be smokers than U.S. white males, but smoking did not differ among the arsenic exposure groups. Exposure-response analysis of smokers was similar to the analysis based on the full subcohort, while analysis of nonsmokers (limited by small group sizes) also showed a similar pattern, but with lower SMRs. The CELs from both analyses of the Anaconda cohort are presented in Table 2-1 and Figure 2-1.

Enterline et al. (1987b) studied the mortality experience from 1949 to 1980 of a cohort of 6,078 white males who had worked for 3 years or more between 1946 and 1976 at one of eight U.S. copper smelters in Arizona, Utah, Tennessee, and Nevada. Lung cancer mortality was significantly increased only in the Utah smelter (SMR=226.7), which had the highest average arsenic exposure concentration (0.069 mg/m^3 vs. 0.007–0.013 mg/m^3 in the other smelters) and also contributed the largest number of cohort members (n=2,288 vs. 189–965 from the other smelters). A nested case-control study showed that arsenic exposure and cigarette smoking were significant risk factors for lung cancer in the smelter workers. Smoking was lower in the Utah smelter workers than in the other smelter workers, but still higher than in the referent Utah population, suggesting that the risk attributable to arsenic in this study population is somewhat lower than indicated by the SMR reported above. The CEL from this study is presented in Table 2-1 and Figure 2-1.

Jarup et al. (1989) reported significantly increased lung cancer mortality (SMR=372, 95% confidence interval [CI]=304–450) based on 106 lung cancer deaths in a cohort of 3,916 male workers employed for $3 months between 1928 and 1967 at the Ronnskar smelter and followed for mortality through 1981. Workers were separated into low, medium, and high arsenic exposure groups with mean time-weighted average exposure estimates of 0.05, 0.2, and 0.4 mg/m^3, respectively. Lung cancer mortality was significantly increased in all three exposure groups in a concentration-related fashion (SMR=201, 353, and 480, respectively). A nested case-control analysis of 102 lung cancer cases and 190 controls from the cohort showed that lung cancer risk increased with increasing arsenic exposure in nonsmokers, light

smokers, and heavy smokers (Jarup and Pershagen 1991). The results demonstrated that arsenic is a risk factor for lung cancer in the smelter workers, but also suggested a greater-than-additive interaction between smoking and arsenic exposure. In this analysis, in contrast to the cohort study, lung cancer risk due to arsenic was increased only in the higher arsenic-exposure groups. Potential explanations for this difference between the cohort and case-control analyses include a higher proportion of smokers in the smelter workers than in the regional referent population in the cohort study, and limited power to detect increased risk in the case-control study due to small group sizes in the dose-response analysis. The CELs from both the cohort and case-control studies are presented in Table 2-1 and Figure 2-1.

Several researchers have examined the histological cell types of lung cancer (epidermoid carcinoma, small cell carcinoma, adenocarcinoma) in arsenic-exposed workers (e.g., Axelson et al. 1978; Newman et al. 1976; Pershagen et al. 1987; Qiao et al. 1997; Wicks et al. 1981). Although the incidence of the various cell types varied from population to population, all studies found an increase in several tumor types. This indicates that arsenic does not specifically increase the incidence of one particular type of lung cancer.

The studies of the ASARCO cohort (Enterline and Marsh 1982; Enterline et al. 1987a, 1995) noted a supralinear exposure-response relationship (i.e., steeper at lower doses) between arsenic exposure and lung cancer mortality. Hertz-Picciotto and Smith (1993) extended this observation to several other occupationally exposed cohorts with quantitative exposure information. The authors suggest that neither toxicokinetic mechanisms nor confounding from age, smoking, or other workplace carcinogens that differ by exposure level are likely explanations for the curvilinearity. Plausible explanations offered include: (1) synergism (with smoking) which varies in magnitude according to the level of arsenic exposure, (2) long-term survivorship at higher exposures among the healthier, less susceptible individuals, and (3) exposure estimate errors that were more prominent at higher-exposure levels as a result of past industrial hygiene sampling or worker protection practices.

Quantitative risk estimates for inhaled inorganic arsenic have been derived using the exposure-response data. EPA derived a unit risk estimate (the excess risk of lung cancer associated with lifetime exposure to 1 $\mu g/m^3$) of 4.3×10^{-3} per ($\mu g/m^3$) based on the dose-response relationships between arsenic exposure and excess lung cancer mortality in workers at the Anaconda smelter in Montana (Brown and Chu 1983a, 1983b, 1983c; Higgins et al. 1982; Lee-Feldstein 1983) and the ASARCO smelter in Tacoma, Washington (Enterline and Marsh 1982; EPA 1984a; IRIS 2000). In some cases, calculations of exposure, as well as the procedures for generating quantitative risk estimates, are quite complex and the

interested reader is referred to the EPA documents (EPA 1981c, 1984a, 1987e, 1996b; IRIS 2000) for a detailed description. Viren and Silvers (1994) re-evaluated the unit risk estimate using the same methods as EPA, but incorporating updated results from the ASARCO smelter (Enterline et al. 1987a; Mazumdar et al. 1989) and the findings from the Swedish smelter (Jarup et al. 1989). Their analysis yielded a revised unit risk of $1.28x10^{-3}$ per ($\mu g/m^3$) that, when pooled with the earlier estimate from the Montana smelter cohort, yielded a composite unit risk of $1.43x10^{-3}$ per ($\mu g/m^3$). This unit risk estimate is a factor of 3 smaller than the EPA's current estimate of $4.3x10^{-3}$ per ($\mu g/m^3$). Figure 2-1 shows the air concentrations that correspond to excess lifetime cancer risks of 10^{-4} to 10^{-7} based on the EPA unit risk estimate.

There have been occasional reports of other types of cancer (i.e., non-respiratory cancer) potentially associated with inhalation exposure to inorganic arsenic, but there is no strong evidence for any of them. For example, Enterline et al. (1995) found significantly increased mortality due to cancer of the large intestine and bone cancer in the ASARCO cohort. However, neither cancer showed any relation to cumulative arsenic exposure, and the purported increase in bone cancer risk was based on a very small number of observations. Bulbulyan et al. (1996) reported an increase in risk of stomach cancer among workers exposed to the highest average arsenic concentrations at a Russian fertilizer plant, but this finding, which was based on a small number of observations and was only marginally statistically significant, was confounded by exposure to nitrogen oxides, which were more convincingly associated with stomach cancer in this study. Wingren and Axelson (1993) reported an association between arsenic exposure and stomach and colon cancer in Swedish glass workers, but this result was confounded by concomitant exposure to other metals. Lee-Feldstein (1983) observed a small, marginally significant increase in digestive tract cancer (SMR=125) in one study of the Anaconda cohort, but this was not found in other studies of this cohort (Lee and Fraumeni 1969; Lee-Feldstein 1986; Welch et al. 1982). Wulff et al. (1996) observed an apparent increase in the risk of childhood cancer (all types combined) in the population living within 20 km of the Ronnskar smelter, but the apparent increase was based on a small number of cases (13 observed vs. 6.7 expected) and was not statistically significant, and exposure to arsenic was confounded by exposure to lead, copper, cadmium, sulfur dioxide, and possibly other emissions such as nickel and selenium. Various case reports have implicated occupational arsenic exposure as a potential contributing factor in workers who developed sinonasal cancer (Battista et al. 1996), hepatic angiosarcoma (Tsai et al. 1998a), and skin cancer (Col et al. 1999; Tsuruta et al. 1998), but provide no proof that inhaled arsenic was involved in the etiology of the observed tumors. Wong et al. (1992) found no evidence that environmental exposure to airborne arsenic produced skin cancer in residents living near the Anaconda smelter.

No studies were located regarding cancer in animals after inhalation exposure to inorganic arsenicals, although several intratracheal instillation studies in hamsters have provided evidence that both arsenite and arsenate can increase the incidence of lung adenomas and/or carcinomas (Ishinishi et al. 1983; Pershagen and Bjorklund 1985; Pershagen et al. 1984a; Yamamoto et al. 1987). These data support the conclusion that inhalation of arsenic may lead to lung cancer in humans.

Organic Arsenicals. No studies were located regarding cancer effects in humans or animals after inhalation exposure to organic arsenicals.

2.2.2 Oral Exposure

There are a large number of studies in humans and animals on the toxic effects of ingested arsenic. In humans, most cases of toxicity have resulted from accidental, suicidal, homicidal, or medicinal ingestion of arsenic-containing powders or solutions or by consumption of contaminated food or drinking water. In some cases, the chemical form is known (e.g., the most common arsenic medicinal was Fowler's solution, which contained 1% potassium arsenite or arsenic trioxide), but in many cases (e.g., exposures through drinking water), the chemical form is not known. In these cases, it is presumed that the most likely forms are either inorganic arsenate [As(+5)], inorganic arsenite [As(+3)], or a mixture. Table 2-3 and Figure 2-3 summarize a number of studies that provide reliable quantitative data on health effects in humans and animals exposed to inorganic arsenicals by the oral route. Similar data for organic arsenicals are listed in Table 2-4 and shown in Figure 2-4. All exposure data are expressed as milligrams of arsenic (as the element) per kilogram body weight per day (mg As/kg/day). These studies and others that provide useful qualitative information are summarized below.

2.2.2.1 Death

Inorganic Arsenicals. There are many case reports of death in humans due to ingestion of high doses of arsenic. In nearly all cases, the most immediate effects are vomiting, diarrhea, and gastrointestinal hemorrhage, and death may ensue from fluid loss and circulatory collapse (Levin-Scherz et al. 1987; Saady et al. 1989). In other cases, death may be delayed and result from the multiple tissue injuries produced by arsenic (Campbell and Alvarez 1989). Some accounts of fatal arsenic poisoning describe both gastrointestinal effects soon after ingestion and extensive damage to multiple organ systems prior to death (Quatrehomme et al. 1992). A precise estimate of the ingested dose is usually not available in acute poisonings, so quantitative information on lethal dose in humans is sparse. The lethal doses ranged from

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
	ACUTE EXPOSURE						
	Death						
1	Human	1 wk (W)				2 (death)	Armstrong et al. 1984 NS
2	Human	once (IN)				121 M (death)	Civantos et al. 1995 As(+5)
3	Human	once (IN)				108 M (death)	Hantson et al. 1996 As(+3)
4	Human	once (IN)				22 M (death)	Levin-Scherz et al. 1987 As(+3)
5	Human	once (IN)				93 M (death)	Quatrehomme et al. 1992 As(+3)
6	Rat (wild Norway)	once (G)				104 (LD50)	Dieke and Richter 1946 As(+3)
7	Rat (Sherman)	once (G)				44 F (LD50)	Gaines 1960 As(+3)

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
8	Rat (Sherman)	once (G)				112 F (LD50)	Gaines 1960 As(+5) calcium arsenate
9	Rat (Sherman)	once (G)				175 F (LD50)	Gaines 1960 As(+5) lead arsenate
10	Rat (Sprague-Dawley)	once (GW)				15 M (LD50)	Harrisson et al. 1958 As(+3)
11	Rat (Sprague-Dawley)	once (F)				145 M (LD50)	Harrisson et al. 1958 As(+3)
12	Rat (CD)	once on Gd9 (GW)				23 F (7/25 dams died)	Stump et al. 1999 As(+3)
13	Mouse (Swiss-Webster)	once (GW)				39 M (LD50)	Harrisson et al. 1958 As(+3)
14	Mouse (C57H46)	once (GW)				26 M (LD50)	Harrisson et al. 1958 As(+3)
15	Mouse (Dba2)	once (GW)				32 M (LD50)	Harrisson et al. 1958 As(+3)

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
16	Mouse (C3H)	once (GW)				26 M (LD50)	Harrisson et al. 1958 As(+3)
17	Mouse (ddY)	once (GW)				26 M (LD50)	Kaise et al. 1985 As(+3)
18	Rabbit (New Zealand)	Gd 6-18 1x/d (GW)				1.49 F (7/20 dams died)	Nemec et al. 1998 As(+5)
	Systemic						
19	Human	1 wk (W)	Gastro		0.2 (vomiting, diarrhea, abdominal pain)	2 M (diffuse inflammation of the GI tract)	Armstrong et al. 1984 NS
			Hemato			0.2 (pancytopenia, leukopenia)	
			Hepatic			0.4 (hepatitis)	
			Renal			0.2 (nephropathy)	
			Ocular		0.2 (periorbital swelling)		
20	Human	once (IN)	Resp			121 M (respiratory distress, lung hemmorhage and edema)	Civantos et al. 1995 As(+5)
			Cardio			121 M (hypotension, ventricular fibrillation, cardiac arrest)	
			Gastro			121 M (ulceration of upper gastrointestinal tract)	

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
21	Human	once (IN)	Cardio			19 F (tachycardia)	Cullen et al. 1995 As (+5)
			Gastro			19 F (profuse vomiting and diarrhea)	
			Hemato	19 F			
			Hepatic	19 F			
			Renal	19 F			
22	Human	once (NS)	Resp			8 M (hemorrhagic bronchitis, pulmonary edema)	Fincher and Koerker 1987 As(+3)
			Cardio			8 M (hypotension, tachycardia, massive cardiomegaly)	
			Gastro			8 M (gastrointestinal bleeding)	
			Hemato			8 M (hemolysis)	
			Musc/skel			8 M (marked atrophy of distal muscle groups)	
			Renal			8 M (acute renal failure)	
			Dermal		8 M (truncal macular rash)		
23	Human	once or twice (W)	Gastro		0.05 (occasional nausea, diarrhea, and abdominal cramps)		Franzblau and Lilis 1989 As(+3) As(+5)
24	Human	once (W)	Gastro			120 M (vomiting and diarrhea)	Goebel et al. 1990 NS
			Renal			120 M (anuria)	
			Dermal		120 M (hyperkeratosis)		

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
25	Human	once (IN)	Gastro		2 F (vomiting)		Hantson et al. 1996 As(+3)
			Hepatic		2 F (slight incr serum bilirubin)		
			Renal		2 F (altered renal function tests)		
26	Human	once (IN)	Gastro			13 M (frequent vomiting, diarrhea)	Kamijo et al. 1998 As(+3)
			Hepatic			13 M (large incr serum bilirubin, ALT, AST, LDH)	
			Dermal		13 M (erythematous eruption)		
			Ocular		13 M (constricted vision)		
27	Human	once (IN)	Resp			22 M (tachypnea, respiratory failure)	Levin-Scherz et al. 1987 As(+3)
			Cardio			22 M (cyanosis, hypotension, tachycardia, ventricular fibrillation)	
			Gastro			22 M (abdominal pain, nausea, diarrhea, massive vomiting, dysphagia, hemorrhage)	
			Hepatic			22 M (large incr serum AST and LDH)	
			Renal			22 M (large incr serum creatinine and BUN indicating acute renal failure)	

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
28	Human	once at wk 30 of pregnancy (IN)	Cardio			6 F (hypotension, rapid pulse)	Lugo et al. 1969 As(+3)
			Gastro			6 F (abdominal pain, vomiting)	
			Hemato		6 F (high leukocyte count, low hematocrit)		
			Renal			6 F (acute renal failure)	
29	Human	2-3 wk (F)	Resp		0.05 (sore throat, rhinorrhea, cough, sputum)		Mizuta et al. 1956 As(+5)
			Cardio			0.05 (abnormal electrocardiogram)	
			Gastro			0.05[b] (nausea, vomiting, diarrhea, occult blood in feces and gastric and duodenal juice)	
			Hemato		0.05 (mild anemia, leukopenia)		
			Musc/skel		0.05 (tender calf muscle)		
			Hepatic		0.05 (mild hepatomegaly, impaired liver function, degenerative lesions)		
			Renal	0.05			
			Dermal		0.05 (pigmentation, itching, desquamation, exanthema)		
			Ocular		0.05 (edema of eyelids, conjunctivitis, central scotoma, neuro-retinitis)		

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
30	Human	once (IN)	Resp	11 M		43 M (shortness of breath, decreased oxygen saturation)	Moore et al. 1994 As(+3)
			Cardio	11 M		43 M (hypotension, asystolic cardiac arrest)	
			Gastro			11 M (profuse diarrhea and vomiting, severe abdominal pain)	
			Hemato	43 M			
			Renal		11 M (incr serum creatinine)	43 M (acute renal failure)	
31	Human	once (IN)	Resp			93 M (pulmonary edema)	Quatrehomme et al. 1992 As(+3)
			Gastro			93 M (ulcero-necrotic hemorrhagic gastritis)	
			Hepatic			93 M (hepatomegaly, diffuse fatty degeneration)	
			Renal			93 M (glomerular congestion)	
			Dermal			93 M (dermoepidermic separation)	
32	Monkey (Rhesus)	13 d 1x/d (IN)	Gastro	3		6 (vomiting, unformed stool, "loss of condition")	Heywood and Sortwell 1979 As(+5)
			Hepatic	3	6 (decr liver glycogen, vacuolation of hepatocytes)		
			Renal	3	6 (dilation of proximal tubules)		

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
33	Rat (Wistar-Barby)	4-14 d 5 d/wk 1x/d (G)	Cardio	2 F	11 F (decr vasoreactivity)		Bekemeier and Hirschelmann 1989 As(+3)
			Gastro	2 F		11 F (diarrhea, bloody stools)	
34	Rat (Sprague-Dawley)	2x (GW)	Resp	14 F			Brown and Kitchin 1996 As(+3)
			Hepatic		0.9 F (slight incr ornithine decarboxylase and heme oxygenase activity in liver)		
			Dermal	14 F			
35	Rat (Sprague-Dawley)	2x (GW)	Hepatic	8 F	24 F (incr heme oxygenase activity in liver)		Brown et al. 1997 As(+5)
36	Rat (CD)	once on Gd9 (GW)	Bd Wt	15 F	23 F (decr body wt gain)		Stump et al. 1999 As(+3)
37	Mouse (CD-1)	Gd 6-15 1x/d (GW)	Bd Wt	12 F	24 F (decr bd wt gain during gestation)		Nemec et al. 1998 As(+5)
38	Mouse (B6C3F1)	1 or 4 d 1x/d (GW)	Hemato	3 M	6 M (decr polychromatic erythrocytes in bone marrow)		Tice et al. 1997 As(+3)

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
39	Rabbit (New Zealand)	Gd 6-18 1x/d (GW)	Bd Wt	0.37 F	1.49 F (loss of body weight during treatment during gestation)		Nemec et al. 1998 As(+5)
	Neurological						
40	Human	1 wk (W)				2 (encephalopathy, peripheral neuropathy)	Armstrong et al. 1984 NS
41	Human	once (IN)				121 M (confusion, brain edema)	Civantos et al. 1995 As(+5)
42	Human	once (IN)				19 F (lethargy)	Cullen et al. 1995 As (+5)
43	Human	once (NS)				8 M (severe, persistent encephalopathy and peripheral neuropathy)	Fincher and Koerker 1987 As(+3)
44	Human	once (W)				120 M (severe polyneuropathy)	Goebel et al. 1990 NS
45	Human	once (IN)				216 M (periperal neuropathy)	Hantson et al. 1996 As(+3)
46	Human	once (IN)				13 M (peripheral neuropathy)	Kamijo et al. 1998 As(+3)

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
47	Human	once (IN)				22 M (agitation, disorientation, paranoia, violent reactions)	Levin-Scherz et al. 1987 As(+3)
48	Human	2-3 wk (F)				0.05 (hypesthesia in legs, abnormal patellar reflex)	Mizuta et al. 1956 As(+5)
49	Human	once (IN)		43 M			Moore et al. 1994 As(+3)
50	Human	once (IN)				93 M (encephalopathy)	Quatrehomme et al. 1992 As(+3)
51	Monkey (Rhesus)	13 d 1x/d (IN)		3		6 (marked salivation, uncontrolled head shaking)	Heywood and Sortwell 1979 As(+5)
52	Rabbit (New Zealand)	Gd 6-18 1x/d (GW)		0.37 F		1.49 F (prostration, ataxia)	Nemec et al. 1998 As(+5)
	Developmental						
53	Human	once at wk 30 of pregnancy (IN)				6 (severe pulmonary hemorrhage that may have contributed to death in premature neonate)	Lugo et al. 1969 As(+3)

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)		Reference Chemical Form
54	Rat (CD)	once on Gd9 (GW)		15		23	(incr post-implantation loss and decr viable fetuses)	Stump et al. 1999 As(+3)
55	Mouse (CD-1)	once during Gd 8-15 (GW)		11		23	(incr fetal mortality, exencephaly)	Baxley et al. 1981 As(+3)
56	Mouse (CD-1)	once during Gd 7-15 (GW)				48	(incr fetal death, decr fetal wt, gross and skeletal malformations)	Hood et al. 1978 As(+5)
57	Mouse (CD-1)	Gd 6-15 1x/d (GW)		12		24	(incr resorptions per litter, decr live fetuses per litter, decr mean fetal wt)	Nemec et al. 1998 As(+5)
58	Hamster (Lak:LVG [SYR])	once during Gd 8-12 (GW)		11		14	(incr fetal mortality, decr fetal wt)	Hood and Harrison 1982 As(+3)
59	Rabbit (New Zealand)	Gd 6-18 1x/d (GW)		0.37		1.49	(incr resorptions per litter, decr live fetuses per litter)	Nemec et al. 1998 As(+5)

INTERMEDIATE EXPOSURE

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Systemic						
60	Human	3 mo (W)	Gastro			0.1 (severe nausea, diarrhea, pain, cramps, vomiting, traces of blood in stool)	Franzblau and Lilis 1989 As(+3) As(+5)
			Hemato			0.1 (anemia, leukopenia)	
			Hepatic			0.1 (large incr AST and ALT)	
			Dermal		0.1 (diffuse erythematous and scaly rash)		
			Ocular		0.1 (swelling and irritation of the eyes, impaired peripheral vision)		
61	Human	0.5-14 yr (W)	Dermal			0.05 (hyperpigmentation with keratosis, possibly pre-cancerous)	Huang et al. 1985 NS
62	Human	4 mo (W)	Gastro			0.06 F (nausea, vomiting, diarrhea)	Wagner et al. 1979 NS
			Hemato			0.06 F (anemia, leukopenia, erythroid hyperplasia of bone marrow)	
			Dermal			0.06 F (persistent extensive hyperkeratosis of palms and soles)	
			Bd Wt			0.06 F (40 lb wt loss)	

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
63	Rat (Wistar-Barby)	4 wk 5 d/wk 1x/d (GW)	Cardio		11 F (decr vasoreactivity)		Bekemeier and Hirschelmann 1989 As(+3)
64	Rat (Sprague-Dawley)	6 wk (W)	Renal		4.7 M (incr relative kidney wt, impaired renal mitochondrial respiration, ultrastructural changes in proximal tubule)		Brown et al. 1976 As(+5)
			Bd Wt	9.4 M	10.9 M (decr body wt gain)		
65	Rat (CD)	6 wk (W)	Hepatic	3 M	6 M (ultrastructural changes in hepatocytes, impaired liver mitochondrial respiration)		Fowler et al. 1977 As(+5)
			Bd Wt	6 M		12 M (final body wt 28% lower than controls)	
66	Rat (CD)	14 d pre-mating thru Gd 19 1 x/d (GW)	Gastro	4 F		8 F (stomach adhesions, eroded luminal epithelium in the stomach)	Holson et al. 2000 As(+3)
			Hepatic	2 F	4 F (incr liver wt)		
			Renal	4 F	8 F (incr kidney wt)		
			Bd Wt	4 F	8 F (decr body wt gain)		
67	Mouse (C57BL)	6 wk (W)	Hepatic	5 M	10 M (ultrastructural changes in hepatocytes, impaired liver mitochondrial respiration)		Fowler and Woods 1979 As(+5)
			Bd Wt	5 M	10 M (decr body wt gain)		

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
68	Mouse (C57BL/6 B6)	14 wk (W)	Hepatic	25 M			Kerkvliet et al. 1980 As(+5)
			Renal	25 M			
69	Dog (Beagle)	26 wk ad lib (F)	Hemato	1.9 F			Neiger and Osweiler 1989 As(+3)
			Hepatic		0.8 F (mild incr serum ALT/AST)		
			Renal	1.9 F			
			Bd Wt	0.8 F	1.5 F (decr body wt gain)	1.9 F (25% decr in body wt)	
Immunological/Lymphoreticular							
70	Mouse (C57BL/6 B6)	14 wk (W)		25 M			Kerkvliet et al. 1980 As(+5)
Neurological							
71	Human	3 mo (W)				0.1 (paresthesia of hands and feet; confusion, disorientation and mental sluggishness)	Franzblau and Lilis 1989 As(+3) As(+5)
72	Human	4 mo (W)				0.06 F (weakness, paresthesia)	Wagner et al. 1979 NS

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
Reproductive							
73	Rat (CD)	14 d pre-mating thru Gd 19 1 x/d (GW)		8 F			Holson et al. 2000 As(+3)
74	Mouse (CD)	3 gen (W)				1 (decr litter size)	Schroeder and Mitchener 1971 As(+3)
Developmental							
75	Rat (CD)	14 d pre-mating thru Gd 19 1 x/d (GW)		4	8 (decr fetal body wt, incr skeletal variations)		Holson et al. 2000 As(+3)
76	Mouse (CD)	3 gen (W)				1 (decr litter size)	Schroeder and Mitchener 1971 As(+3)
CHRONIC EXPOSURE							
Death							
77	Human	2-7 yr children (W)				0.05 (death)	Zaldivar and Guillier 1977 NS

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
78	Human	22 yr (W)				0.014 M (death)	Zaldivar et al. 1981 NS
79	Monkey (Rhesus)	1 yr (IN)				3 (2/7 died)	Heywood and Sortwell 1979 As(+5)
80	Rat (Wistar)	27 mo (F)				30 (incr mortality)	Kroes et al. 1974 As(+5) lead arsenate
81	Mouse (CD)	2 yr (W)				1 (incr mortality, decr life span)	Schroeder and Balassa 1967 As(+3)
82	Dog (Beagle)	2 yr (F)				2.4 (6/6 died)	Byron et al. 1967 As(+3)
83	Dog (Beagle)	2 yr (F)				2.4 (1/6 died)	Byron et al. 1967 As(+5)
	Systemic						
84	Human	NS (W)	Resp		0.032 (cough)		Ahmad et al. 1997 NS
			Dermal			0.032 (melanosis, keratosis, hyperkeratosis, and depigmentation)	
			Ocular			0.032 (chronic conjunctivitis)	

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL				Reference Chemical Form
					Less Serious (mg/kg/day)		Serious (mg/kg/day)		
85	Human	4 yr (IN)	Dermal				0.1 F	(de-pigmentation with hyperkeratosis, possibly pre-cancerous)	Bickley and Papa 1989 As(+3)
86	Human	NS (W)	Cardio				0.014	(gangrene of feet)	Biswas et al. 1998 NS
			Dermal				0.014	(melanosis and keratosis of hand palms and foot soles)	
87	Human	12 yr (W)	Cardio				0.02	(Raynaud's disease, gangrene of toes)	Borgono and Greiber 1972 NS
			Gastro		0.02	(diarrhea, abdominal pain)			
			Dermal				0.02	(abnormal pigmentation with hyperkaratosis, possibly pre-cancerous)	
88	Human	11-15 yr (W)	Dermal		0.01	(hypo- and hyperpigmentation)			Borgono et al. 1980 NS
89	Human	continuous (W)	Gastro	0.0004	0.022	(gastrointestinal irritation, diarrhea, nausea)			Cebrian et al. 1983 As(+5)
			Dermal	0.0004			0.022	Pigmentation changes with hyperkeratosis (possibly pre-cancerous)	

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL				Reference Chemical Form
					Less Serious (mg/kg/day)		Serious (mg/kg/day)		
90	Human	1-11 yr (W)	Hepatic		0.046	(hepatomegaly)			Chakraborty and Saha 1987 NS
			Dermal				0.046	(pigmentation changes with keratosis, possibly pre-cancerous)	
91	Human	continuous (W)	Cardio				0.064	(Blackfoot disease)	Chen et al. 1988b NS
92	Human	>10 yr (W)	Cardio	0.0008			0.022	(increased risk of ischemic heart disease mortality)	Chen et al. 1996 NS
93	Human	NS (W)	Cardio				0.002	(incr prevalence of cerebrovascular disease and cerebral infarction)	Chiou et al. 1997 NS
94	Human	3-7 yr (W)	Cardio				0.05	(Blackfoot disease)	Foy et al. 1992 NS
			Dermal				0.05	(melanosis with hyperkeratosis, possibly pre-cancerous)	
95	Human	2-6 yr (IN)	Hepatic				0.08 M	(cirrhosis, ascites)	Franklin et al. 1950 As(+3)
			Dermal				0.08 M	(pigmentation with hyperkeratosis, possibly pre-cancerous)	

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL				Reference Chemical Form
					Less Serious (mg/kg/day)		Serious (mg/kg/day)		
96	Human	NS (W)	Hepatic	0.004			0.014	(hepatomegaly)	Guha Mazumder et al. 1988 NS
			Dermal	0.004			0.014	(pigmentation changes with hyperkaratosis, possibly pre-cancerous)	
97	Human	1-20 yr (W)							Guha Mazumder et al. 1988 NS
			Gastro		0.06	(abdominal pain)			
			Hemato		0.06	(anemia)			
			Hepatic				0.06	(hepatomegaly, fibrosis)	
			Dermal				0.06	(hyperpigmentation with hyperkeratosis, possibly pre-cancerous)	
98	Human	NS (W)	Dermal	0.0016			0.009	(hyperpigmentation with (keratosis, possibly pre-cancerous)	Guha Mazumder et al. 1998a NS
99	Human	10 yr (W)	Gastro	0.00065					Harrington et al. 1978 NS
			Hemato	0.00065					
			Dermal	0.00065					

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
100	Human	NS (W)	Hepatic	0.0008	0.006 (incr serum alkaline phosphatase and bilirubin)		Hernandez-Zavala et al. 1998 NS
101	Human	NS (W)	Cardio			0.067 (ischemic heart disease)	Hsueh et al. 1998 NS
102	Human	0.5-14 yr (W)	Dermal			0.05 (hyperpigmentation with keratosis, possibly pre-cancerous)	Huang et al. 1985 NS
103	Human	15 yr (IN)	Gastro			0.03 M (hematemesis, hemoperitoneum, melena)	Lander et al. 1975 As(+3)
			Dermal			0.03 M (hyperkeratosis - possibly pre-cancerous)	
104	Human	NS (W)	Cardio	0.004		0.005 (cyanosis of extremities, palpitations/chest discomfort)	Lianfang and Jianzhong 1994 NS
			Dermal	0.004		0.005 (keratosis, hyperpigmentation, depigmentation)	
105	Human	3-22 yr (IN)	Gastro			0.05 M (gastrointestinal hemorrhages)	Morris et al. 1974 As(+3)
			Hepatic			0.05 M (vascular fibrosis, portal hypertension)	
			Dermal			0.05 M (hyperpigmentation with keratoses, possibly pre-cancerous)	

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
106	Human	15 yr (IN)	Hepatic			0.05 F (central fibrosis)	Piontek et al. 1989 As(+3)
			Dermal			0.05 F (hyperkeratosis, possibly pre-cancerous)	
107	Human	NS (W)	Endocr			0.11 (diabetes mellitus)	Rahman et al. 1998 NS
108	Human	NS (W)	Cardio	0.018		0.055 (hypertension)	Rahman et al. 1999 NS
109	Human	28 mo (IN)	Cardio	0.06 F			Silver and Wainman 1952 As(+3)
			Gastro		0.06 F (intermittent, progressively severe nausea, cramps, and diarrhea)		
			Hemato	0.06 F			
			Hepatic		0.06 F (hepatomegaly, fatty liver)		
			Renal	0.06 F			
			Dermal			0.06 F (melanosis with hyperkeratosis, possibly pre-cancerous)	
			Ocular		0.06 F (conjunctival injection, periocular edema)		

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
110	Human	≥ 5 yr (W)	Hemato	0.006 M 0.007 F			Southwick et al. 1981 NS
			Dermal	0.0009 M 0.001 F			
111	Human	55 yr (IN)	Hepatic			0.03 M (portal fibrosis and hypertension, bleeding from esophageal varices)	Szuler et al. 1979 As(+3)
			Dermal			0.03 M (hyperpigmentation with hyperkeratosis, possibly pre-cancerous)	
112	Human	45 yr (W)	Cardio			0.014 (Blackfoot disease)	Tseng 1977 NS
113	Human	NS (W)	Cardio			0.014 (Blackfoot disease)	Tseng 1989 NS
114	Human	≥ 45 yr (W)	Dermal	0.0008[c] M	0.014 M (hyperkeratosis and hyperpigmentation)		Tseng et al. 1968 NS
115	Human	≥ 30 yr (W)	Cardio		0.064 M (deficits in cutaneous microcirculation of the toes)		Tseng et al. 1995 As(+3)
116	Human	52.6 yr (avg) (W)	Cardio	0.016		0.031 (peripheral vascular disease)	Tseng et al. 1996 NS

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
117	Human	16 mo (IN)	Resp	0.1 M			Wade and Frazer 1953
							As(+3)
			Cardio	0.1 M			
			Hemato	0.1 M			
			Hepatic		0.1 M (liver enlargment)		
			Dermal			0.1 M (hyperkeratosis, hyperpigmentation with hyperkeratosis, possibly pre-cancerous)	
118	Human	12 yr (W)	Resp		0.015 M (bronchitis, bronchiectasis)		Zaldivar 1974
					0.018 F		NS
			Cardio			0.015 M (Raynaud's disease, thrombosis)	
						0.018 F	
			Gastro		0.015 M (diarrhea)		
					0.018 F		
			Dermal		0.015 M (scaling of skin, hyperkeratosis, leukoderma, melanoderma)		
					0.018 F		
			Bd Wt		0.015 M (unspecified decr body wt)		
					0.018 F		

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
119	Human	30-33 yr (W)	Dermal			0.015 M (hyperkeratosis of foot, possibly pre-cancerous)	Zaldivar 1974 NS
120	Human	NS (W)	Dermal			0.063 (hyperpigmentation with keratoses, possibly pre-cancerous)	Zaldivar 1977 NS
121	Human	1-39 yr (W)	Cardio			0.06 (arterial thickening, Raynaud's disease)	Zaldivar and Guillier 1977 NS
122	Human	2-7 yr children (W)	Resp			0.08 (inflammation of bronchi and larynx, bronchopneumonia)	Zaldivar and Guillier 1977 NS
			Cardio			0.05 (vascular spasms, thrombosis, ischemia, hypotension, cardiac failure)	
			Gastro			0.05 (nause, vomiting, diarrhea, intestinal hemorrhage)	
			Hemato			0.05 (anemia)	
			Hepatic			0.08 (cirrhosis)	
			Renal		0.08 (cloudy swelling in kidneys)		
			Dermal			0.05 (hyperkeratosis of palms and soles, melanoderma, leukoderma)	

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL				Reference Chemical Form
					Less Serious (mg/kg/day)		Serious (mg/kg/day)		
123	Rat (Osborne-Mendel)	2 yr (F)	Resp	20					Byron et al. 1967 As(+3)
			Cardio	20					
			Gastro	20					
			Hemato	9	20	(slight transient decr in Hb and H values)			
			Hepatic	4			9	(enlarged bile duct, bile duct proliferation)	
			Renal	9	20	(pigmentation)			
			Bd Wt	2	4	(decr body wt gain)			
124	Rat (Osborne-Mendel)	2 yr (F)	Resp	30					Byron et al. 1967 As(+5)
			Cardio	30					
			Gastro	30					
			Hemato	30					
			Hepatic	9	20	(enlarged bile duct)			
			Renal	9	20	(pigmentation, cysts)			
			Bd Wt		2	(decr body wt gain in females)			

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
125	Rat (Wistar)	27 mo (F)	Resp	7			Kroes et al. 1974 As(+5)
			Cardio	7			
			Gastro	7			
			Hemato	7			
			Musc/skel	7			
			Hepatic	7			
			Renal	7			
			Endocr	7			
			Bd Wt		7 (decr body wt gain)		
126	Rat (Wistar)	27 mo (F)	Resp	30			Kroes et al. 1974 As(+5) lead arsenate
			Cardio	30			
			Gastro	30			
			Hemato	7	30 (slight anemia)		
			Musc/skel	30			
			Hepatic	7		30 (enlarged bile duct with extensive dilatation and inflammation)	
			Renal	30			
			Endocr	30			
			Bd Wt	7	30 (decr body wt gain)		

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
127	Rat (Long-Evans)	3 yr (W)	Resp	0.6			Schroeder et al. 1968 As(+3)
			Cardio	0.6			
			Hepatic	0.6			
			Renal	0.6			
			Dermal	0.6			
			Bd Wt	0.6			
128	Mouse (CD)	2 yr (W)	Bd Wt		1 (decr body wt gain after the first 6 mo of the study)		Schroeder and Balassa 1967 As(+3)
129	Dog (Beagle)	2 yr (F)	Resp	2.4			Byron et al. 1967 As(+3)
			Cardio	2.4			
			Gastro	1		2.4 (bleeding in the gut)	
			Hemato	1	2.4 (slight to moderate anemia)		
			Hepatic	1	2.4 (hemosiderin deposits in hepatic macrophages)		
			Renal	2.4			
			Bd Wt	1		2.4 (44-61% wt loss)	

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
130	Dog (Beagle)	2 yr (F)	Resp	2.4			Byron et al. 1967 As(+5)
			Cardio	2.4			
			Gastro	2.4			
			Hemato	1	2.4 (mild anemia)		
			Hepatic	1	2.4 (pigmentation in hepatic macrophages)		
			Renal	2.4			
			Bd Wt	1		2.4 (marked decr wt gain)	
	Neurological						
131	Human	3-7 yr (W)				0.11 F (wrist weakness)	Foy et al. 1992 NS
132	Human	1-20 yr (W)			0.06 (tingling of hands and feet)		Guha Mazumder et al. 1988 NS
133	Human	10 yr (W)		0.00065			Harrington et al. 1978 NS
134	Human	continuous (W)		0.0014		0.04 (functional denervation)	Hindmarsh et al. 1977 NS

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
135	Human	NS (W)		0.004	0.005 (fatigue, headache, dizziness, insomnia, nighmare, numbness)		Lianfang and Jianzhong 1994 NS
136	Human	28 mo (IN)				0.06 F (paresthesia)	Silver and Wainman 1952 As(+3)
137	Human	≥ 5 yr (W)		0.006 M 0.007 F			Southwick et al. 1981 NS
138	Human	55 yr (IN)			0.03 M (absent ankle jerk reflex and vibration sense in legs)		Szuler et al. 1979 As(+3)
	Cancer						
139	Human	continuous (W)				0.022 (CEL: skin cancer)	Cebrian et al. 1983 As(+5)
140	Human	continuous (W)				0.064 (CEL: bladder, lung and liver cancers)	Chen et al. 1986 NS
141	Human	continuous (W)				0.064 (CEL: malignant neoplasms of the bladder, skin, lung and liver)	Chen et al. 1988b NS
142	Human	2 wk-12 yr (IN)				3.67 (CEL: bladder cancer risk)	Cuzick et al.1992 As(+3)

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL			Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
143	Human	NS (W)				0.0011	(CEL: lung cancer)	Ferreccio et al. 1998 NS
144	Human	NS (W)				0.052	(CEL: incr incidence of transitional cell carcinomas of the bladder, kidney, & ureters and all urethral cancer)	Guo et al. 1997 NS
145	Human	>1 yr (W)				0.0075	(CEL: basal or squamous skin carcinoma)	Haupert et al. 1996 NS
146	Human	16 yr (avg) (IN)				0.04 M	(CEL: basal cell and squamous cell carcinomas of the skin, small cell and squamous cell carcinoma of the lung)	Luchtrath 1983 As(+5)
147	Human	60 yr continuous (W)				0.038	(CEL: intraepidermal carcinoma)	Tseng 1977 NS
148	Human	≥ 45 yr (W)				0.014	(CEL: squamous cell carcinoma of the skin)	Tseng et al. 1968 NS
149	Human	~5 yr (W)				0.033	(CEL: lung, urinary tract cancer)	Tsuda et al. 1995a As(+3)

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
150	Human	12 yr (W)				0.015 M (CEL: squamous cell carcinoma of the skin) 0.018 F (CEL: squamous cell carcinoma of the skin)	Zaldivar 1974 NS
151	Human	22-34 yr (W)				0.014 M (CEL: basal cell and squamous cell carcinomas of the skin, hemangioendothelioma of the liver)	Zaldivar et al. 1981 NS

[a]The number corresponds to entries in Figure 2-3.
[b]Used to derive provisional acute oral minimal risk level (MRL) of 0.005 mg/kg/day; dose divided by an uncertainty factor of 10 (for extrapolation from a LOAEL to a NOAEL).
[c]Used to derive chronic oral minimal risk level (MRL) of 0.0003 mg/kg/day; dose divided by an uncertainty factor of 3 (for human variability).

avg = average; ALT = alanine aminotransferase; AST = aspartate aminotransferase; Bd Wt = body weight; BUN = blood urea nitrogen; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); decr = decreased; Endocr = endocrine; (F) = feed; F = female; Gastro = gastrointestinal; GI = gastrointestinal; (GW) = gavage in water; gen = generation; Gd = gestation day; Gn pig = guinea pig; Hb = hemoglobin; Hct = hematocrit; Hemato = hematological; hr = hour(s); IN = ingestion; incr = increased; LD50 = lethal dose, 50% kill; LDH = lactate dehydrogenase; LOAEL = lowest-observable-adverse-effect level; M = male; Metab = metabolic; mo = month(s); NOAEL = no-observable-adverse-effect level; NS = not specified; Resp = respiratory; (W) = water; wk = week(s); wt = weight; yr = year(s)

Figure 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral

Acute (≤14 days)

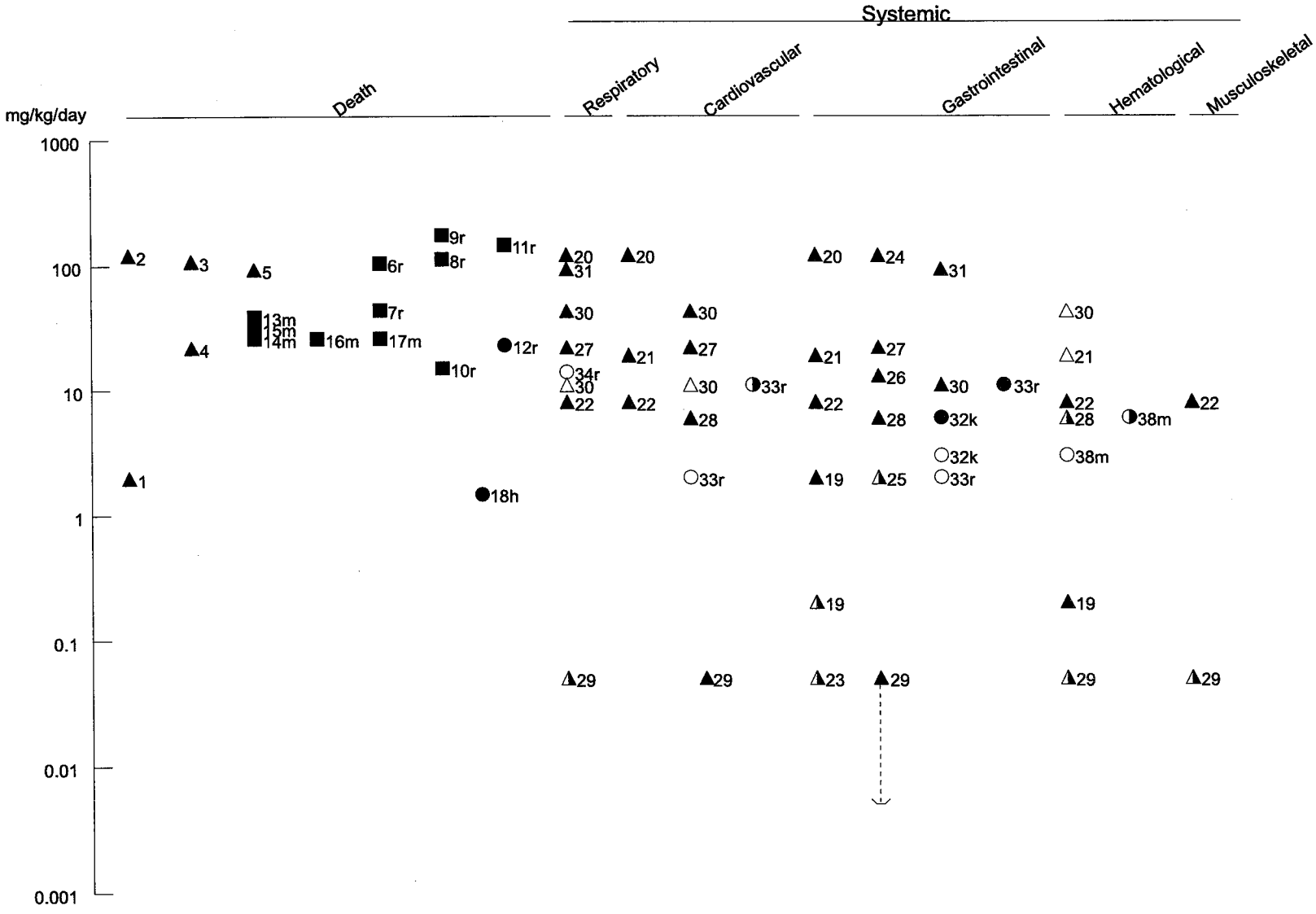


Figure 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (*continued*)

Acute (≤14 days)

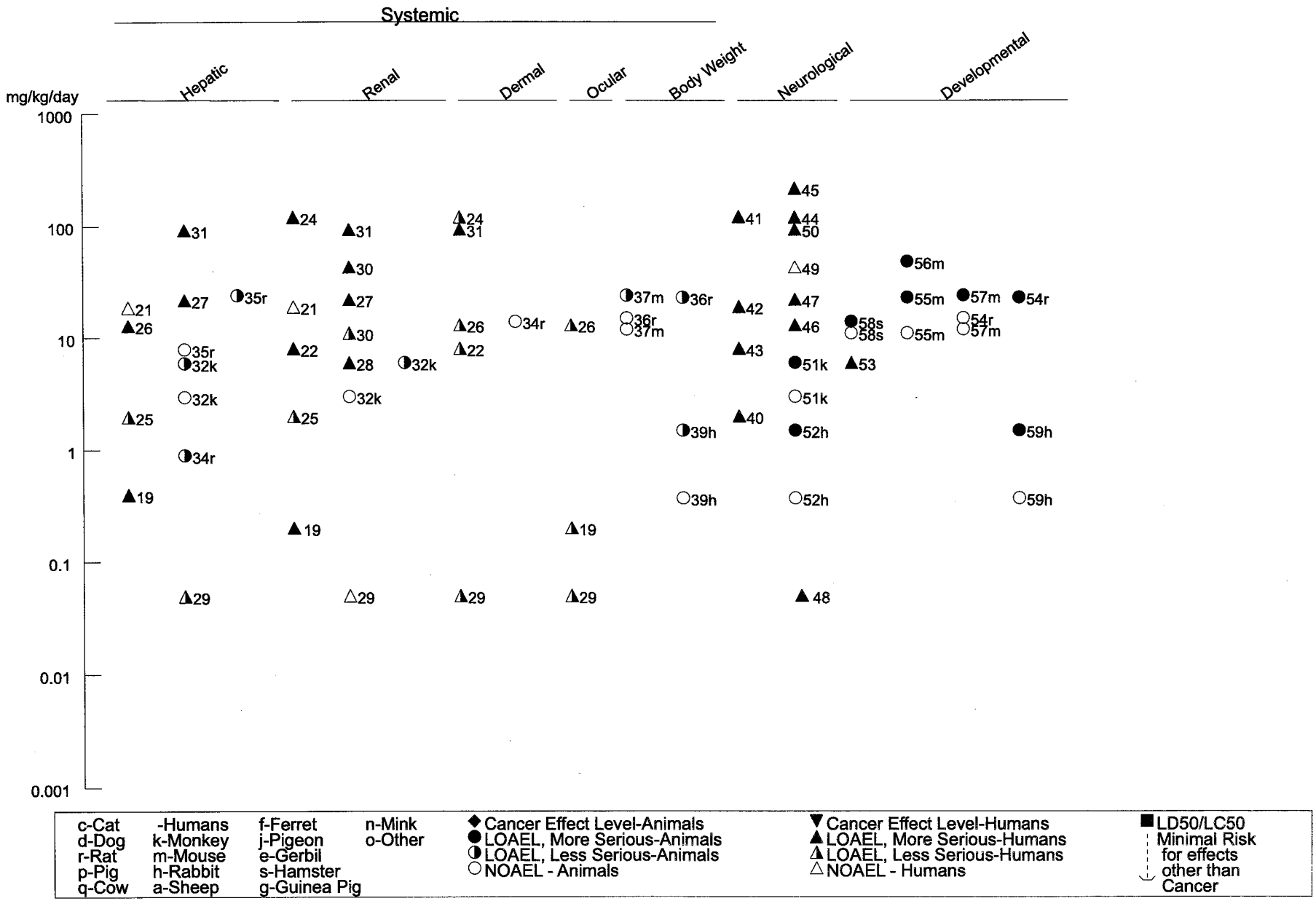
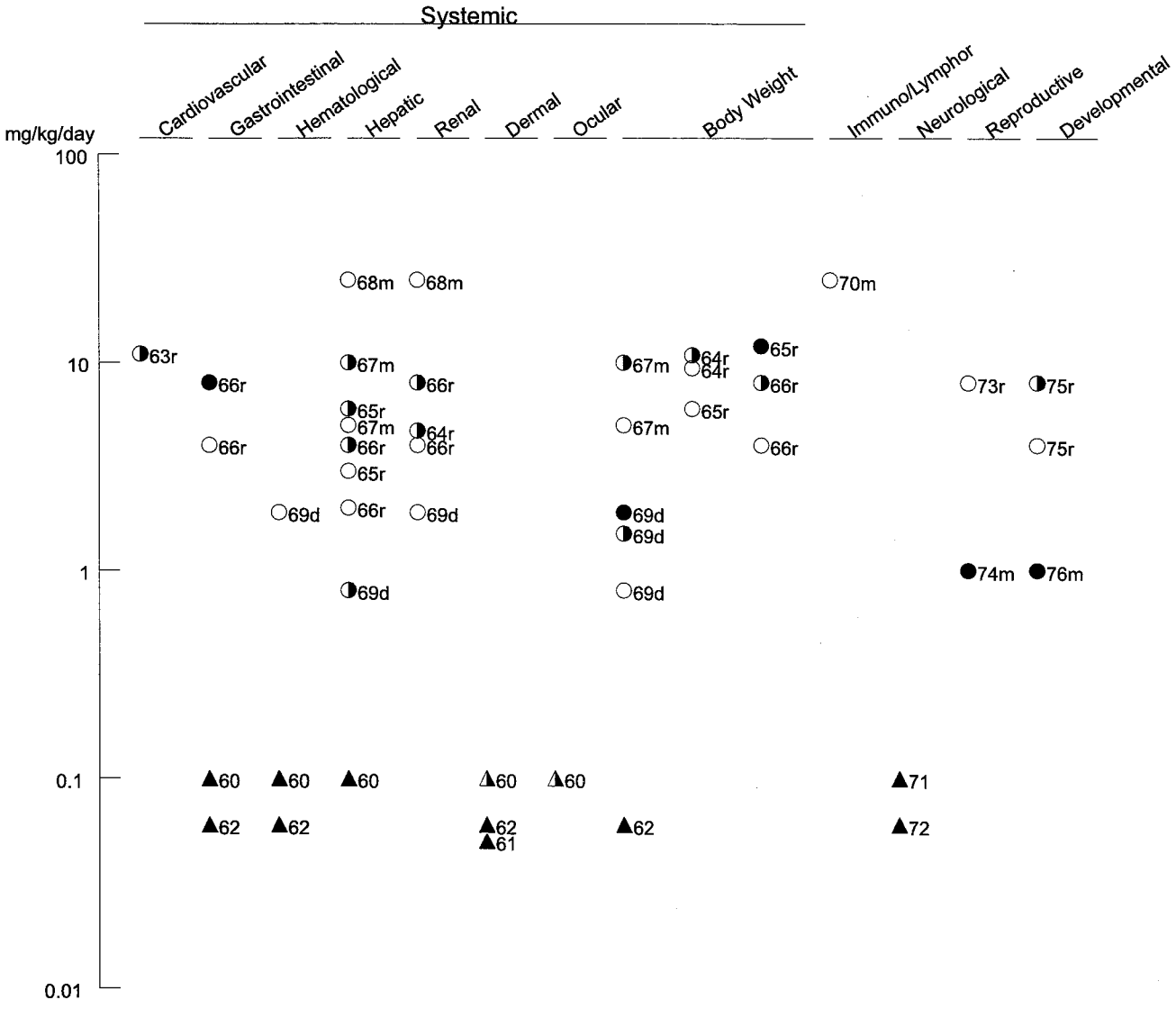


Figure 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (*continued*)

Intermediate (15-364 days)



c-Cat	-Humans	f-Ferret	n-Mink	◆ Cancer Effect Level-Animals	▼ Cancer Effect Level-Humans	■ LD50/LC50
d-Dog	k-Monkey	j-Pigeon	o-Other	● LOAEL, More Serious-Animals	▲ LOAEL, More Serious-Humans	Minimal Risk for effects other than Cancer
r-Rat	m-Mouse	e-Gerbil		◑ LOAEL, Less Serious-Animals	◮ LOAEL, Less Serious-Humans	
p-Pig	h-Rabbit	s-Hamster		○ NOAEL - Animals	△ NOAEL - Humans	
q-Cow	a-Sheep	g-Guinea Pig				

Figure 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (*continued*)

Chronic (≥365 days)

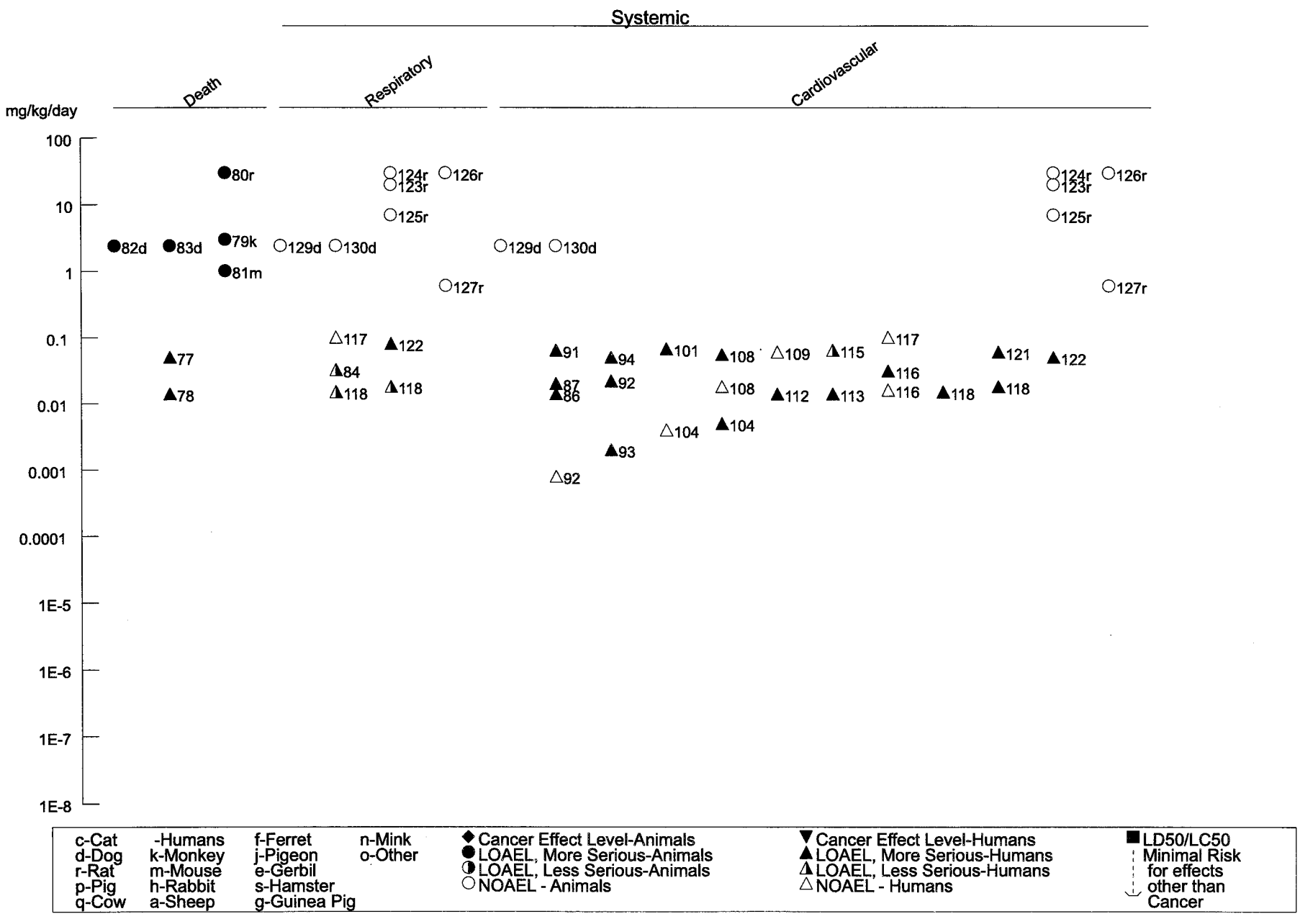


Figure 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (*continued*)

Chronic (≥365 days)

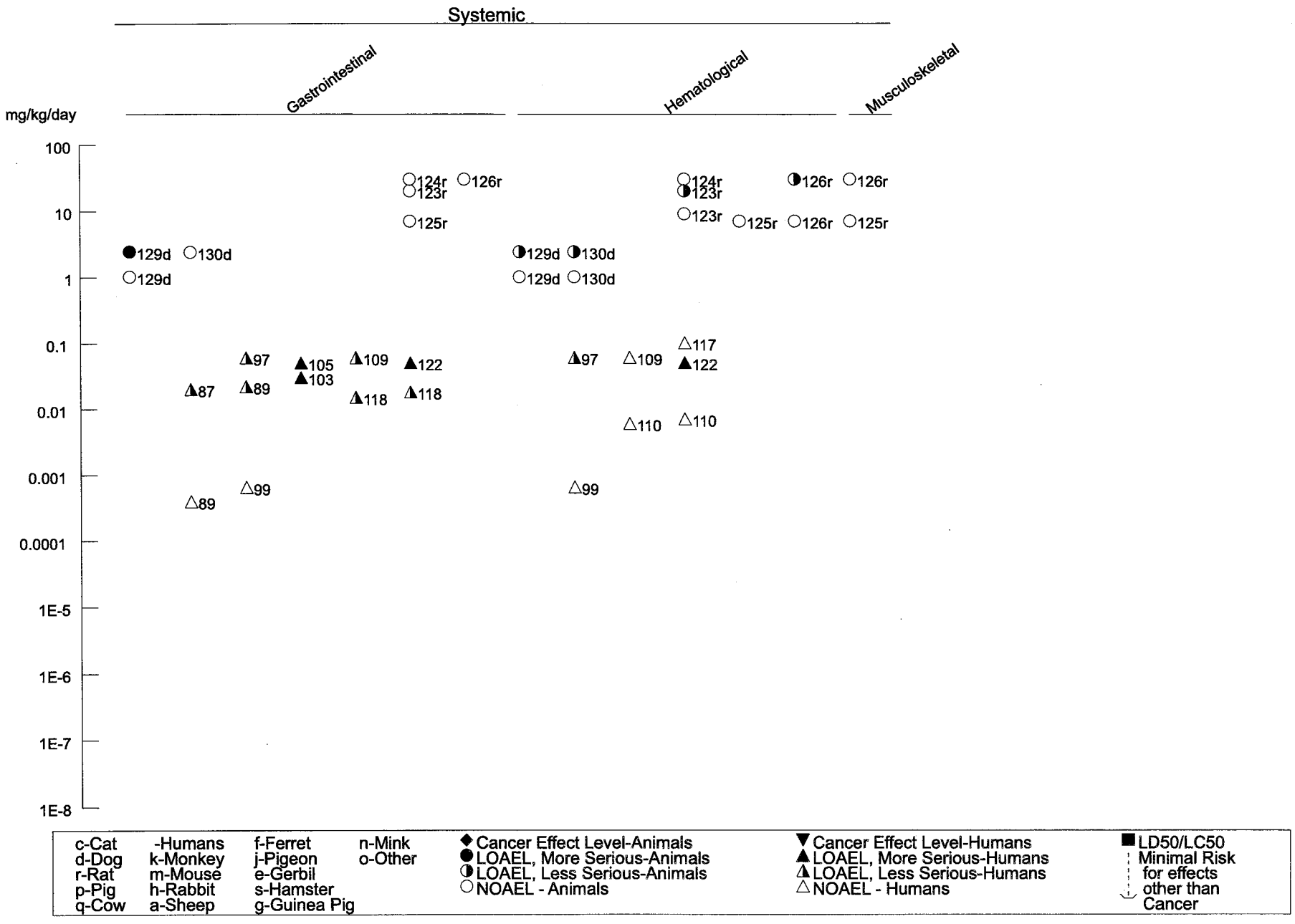


Figure 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (*continued*)

Chronic (≥365 days)

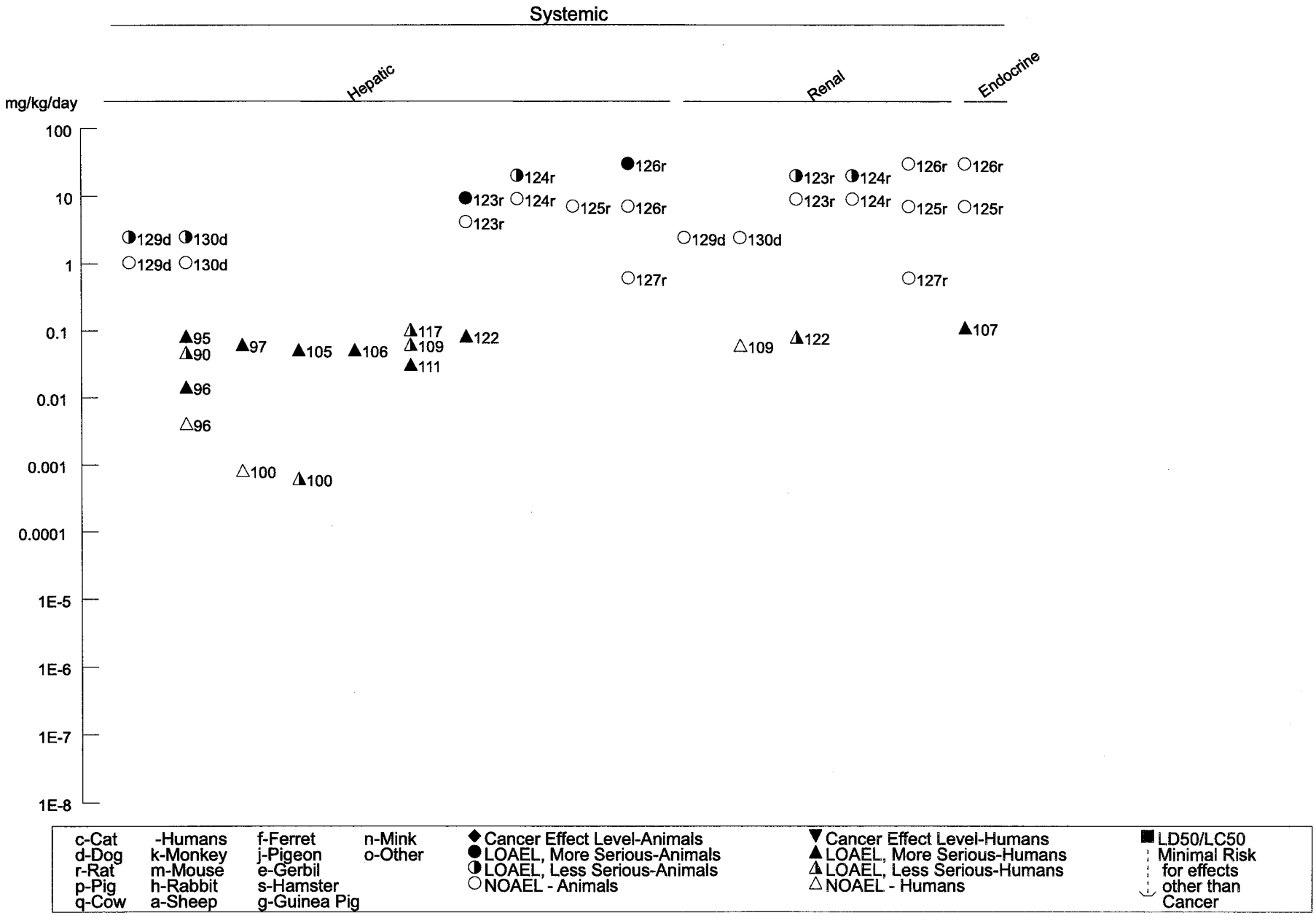


Figure 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (*continued*)

Chronic (≥365 days)

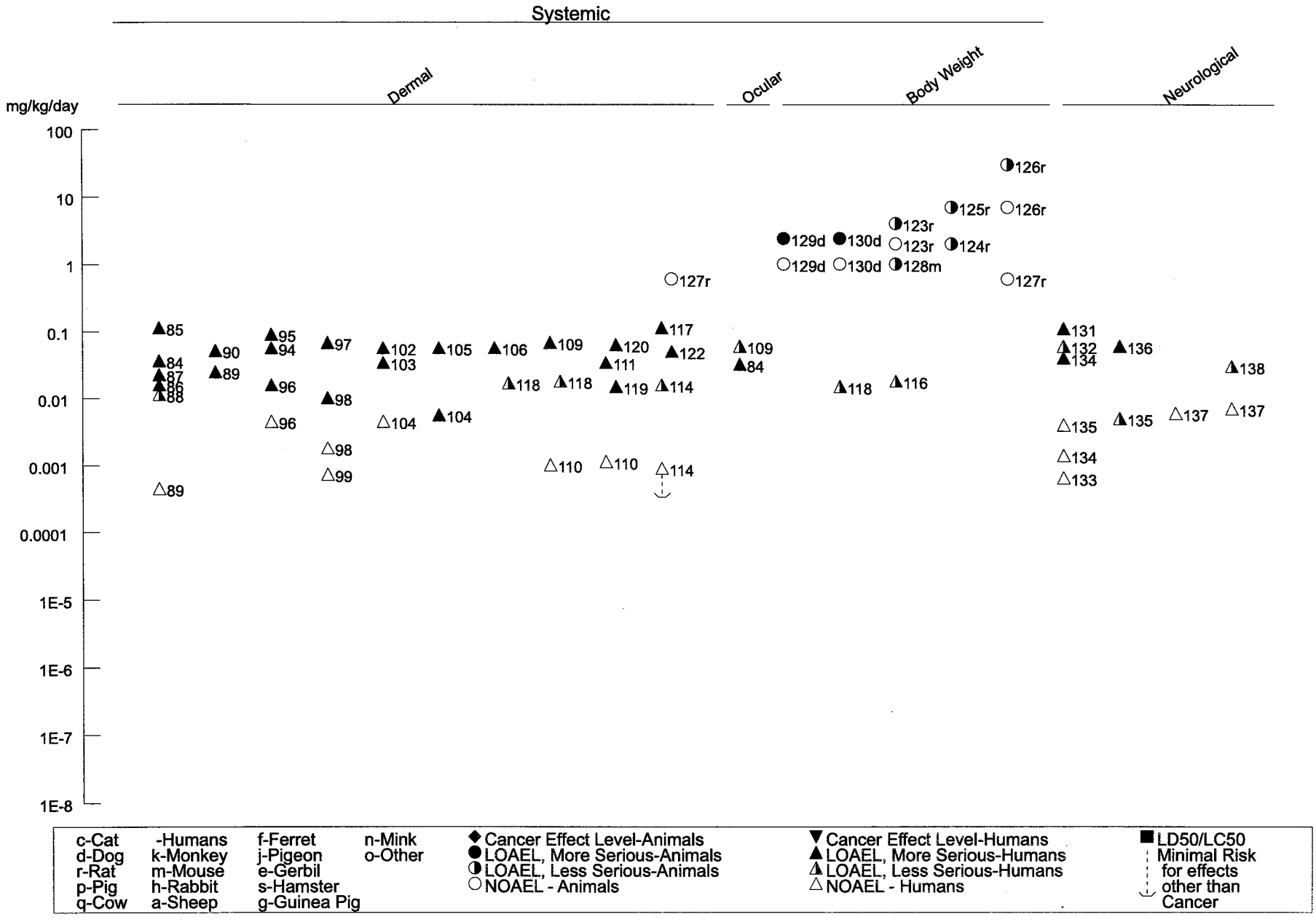


Figure 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (*continued*)

Chronic (≥365 days)

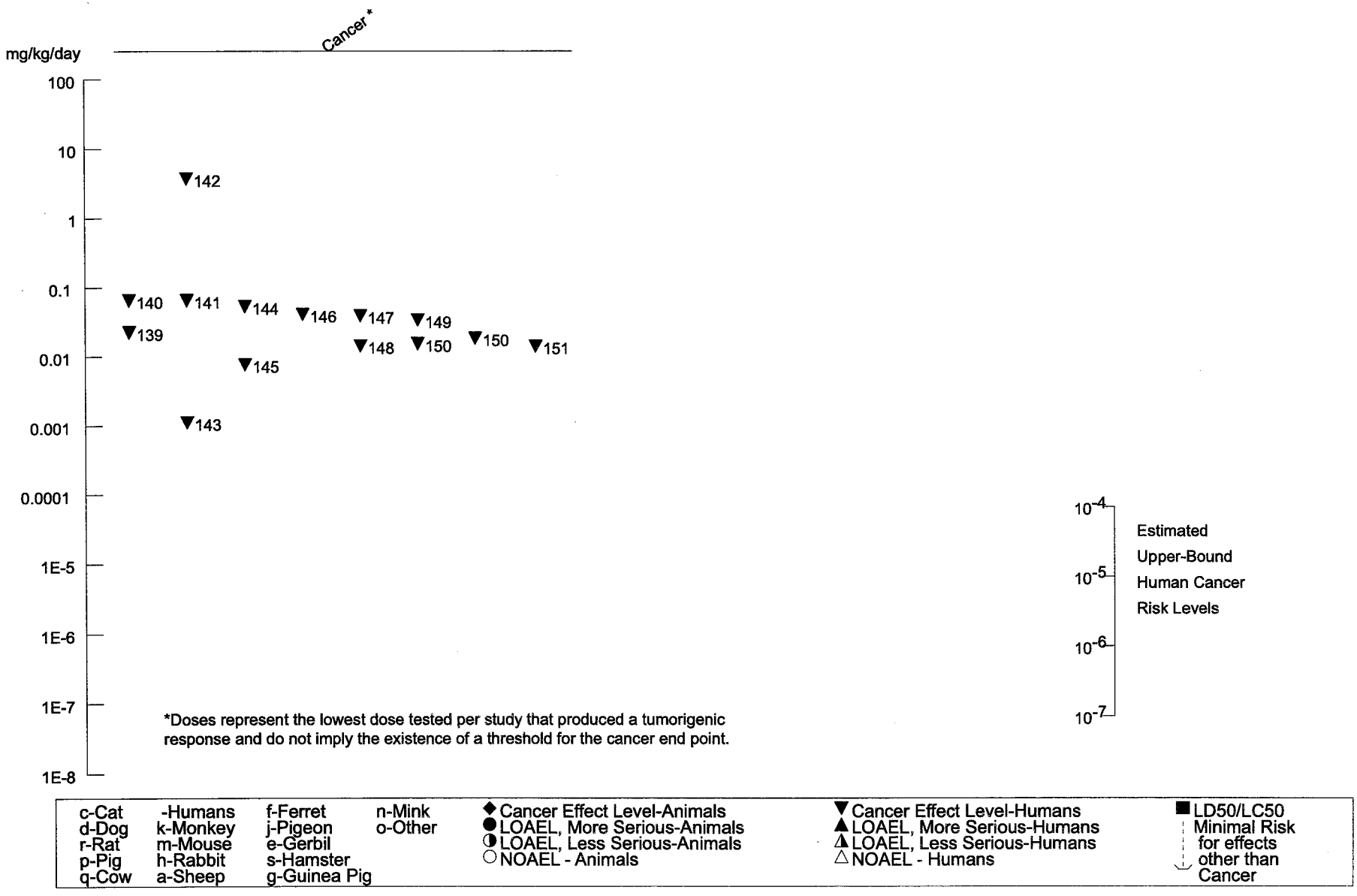


Table 2-4. Levels of Significant Exposure to Organic Arsenic - Oral

Key to[a] figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
	ACUTE EXPOSURE						
	Death						
1	Rat (Holtzman)	once (GW)				44 (LD50)	Kerr et al. 1963 ROX
2	Rat (Fischer- 344)	9d 1x/d (G)				61 (1/3 died)	Murai et al. 1993 DMA
3	Rat (Fischer- 344)	once (GO)				21.4 F (2/5 died; LD50=23.1 mg As/kg) 42.7 M (5/5 died)	NTP 1989b ROX
4	Rat (Fischer- 344)	14 d (F)				36.46 M (3/5 died) 41.02 F (5/5 died)	NTP 1989b ROX
5	Rat (CD)	10 d Gd 7-16 1x/d (GW)				21.7 F (4% mortality)	Rogers et al. 1981 DMA
6	Mouse (ddY)	once (GW)				652 M (LD50)	Kaise et al. 1989 DMA
7	Mouse (ddY)	once (GW)				963 M (LD50)	Kaise et al. 1989 MMA

Table 2-4. Levels of Significant Exposure to Organic Arsenic - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
8	Mouse (B6C3F1)	14 d (F)				48.4 (2/5 males died; 5/5 females died)	NTP 1989b ROX
9	Mouse (B6C3F1)	once (GO)				69.5 F (LD50) 85.4 M (5/5 died)	NTP 1989b ROX
10	Mouse (CD-1)	10 d Gd 7-16 1x/d (GW)				217 F (3% mortality)	Rogers et al. 1981 DMA
11	Dog (Mongrel)	once (C)				14.2 (LD50)	Kerr et al. 1963 ROX
12	Rabbit (New Zealand)	once (GW)				47 M (LD50)	Jaghabir et al. 1988 MMA
	Systemic						
13	Human	once (IN)	Cardio		77.1 M (sinus tachycardia)		Lee et al. 1995 DMA
			Gastro		77.1 M (vomiting, abdominal pain, hyperactive bowel, watery garlic-smelling stools)		
			Hemato	77.1 M			
			Hepatic	77.1 M			

Table 2-4. Levels of Significant Exposure to Organic Arsenic - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
14	Human	once (IN)	Resp	793 M			Shum et al. 1995 MSMA
			Cardio	793 M			
			Gastro		793 M (vomiting)		
			Hepatic	793 M			
			Renal	793 M			
15	Rat (Fischer- 344)	14 d (F)	Hemato	18.23 M 20.51 F	36.46 M 41.02 F (cyanosis of the eye)		NTP 1989b ROX
			Bd Wt	4.56 M 41.02 F	9.11 M (22% reduced body weight)		
16	Rat (CD)	10 d Gd 7-16 1x/d (GW)	Bd Wt			21.7 F (27% decreased maternal weight gain)	Rogers et al. 1981 DMA
17	Mouse (B6C3F1)	24 hr 1 or 2x (GW)	Resp		391 F (decr lung ODC)		Ahmad et al. 1999 DMA
			Hepatic		391 F (decr liver GSH, GSSG, CYP-450 and ODC; incr serum ALT)		
18	Mouse (ddY)	once (GW)	Resp			489 M (respiratory arrest)	Kaise et al. 1989 DMA
			Gastro		954 M (diarrhea, slight congestion of the intestion)		

Table 2-4. Levels of Significant Exposure to Organic Arsenic - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
19	Mouse (ddY)	once (GW)	Resp			963 M (respiratory arrest)	Kaise et al. 1989 MMA
			Gastro		1177 M (diarrhea, slight congestion of the small intestine)		
20	Mouse (B6C3F1)	14 d (F)	Hemato	5.8	12.1 (pale skin)		NTP 1989b ROX
			Bd Wt	48.4			
21	Mouse (CD-1)	10 d Gd 7-16 1x/d (GW)	Bd Wt			109 F (26% decreased maternal weight gain)	Rogers et al. 1981 DMA
22	Dog (Mongrel)	once (C)	Resp			14.2 (localized hemorrhage in lung)	Kerr et al. 1963 ROX
			Gastro			14.2 (vomiting; hemorrhages in the pyloric portion of the stomach, colon and cecum)	
			Hepatic			14.2 (generalized icterus)	
			Renal			14.2 (hematuria, congested kidney)	
			Other		14.2 (bloody mucus in feces)		
23	Rabbit (New Zealand)	once (GW)	Gastro		28 M (constipation, diarrhea)		Jaghabir et al. 1988 MMA
			Renal		28 M (oliguri a)		

Table 2-4. Levels of Significant Exposure to Organic Arsenic - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
Neurological							
24	Rat (Fischer- 344)	14 d (F)		4.56	9.11 M (slight inactivity)		NTP 1989b ROX
				5.13	10.25 F		
25	Mouse (ddY)	once (GW)				954 M (increased startle reflex; ataxia)	Kaise et al. 1989 DMA
26	Mouse (B6C3F1)	14 d (F)		5.8	12.1 (slight inactivity; ruffled fur)		NTP 1989b ROX
27	Rabbit (New Zealand)	once (GW)			28 M (weakness, loss of appetite)		Jaghabir et al. 1988 MMA
Developmental							
28	Rat (CD)	10 d Gd 7-16 1x/d (GW)		8.1		16.3 (malformed palates in 15%)	Rogers et al. 1981 DMA
29	Mouse (CD-1)	10 d Gd 7-16 1x/d (GW)		109		217 (18% decrease in fetal weight, delayed ossification, cleft palate in 12/28; irregular palatine rugae in 4.8%)	Rogers et al. 1981 DMA

Table 2-4. Levels of Significant Exposure to Organic Arsenic - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
INTERMEDIATE EXPOSURE							
Death							
30	Rat (Holtzman)	13 wk (F)				5.7 (10/12 died)	Kerr et al. 1963 ROX
31	Rat (Fischer- 344)	4 wk 5 d/wk 1x/d (G)				31 (50% survival in males; 20% survival in females)	Murai et al. 1993 DMA
32	Rat (Fischer- 344)	13 wk ad lib (F)				18.23 M (3/10 died) 20.51 F (2/10 died)	NTP 1989b ROX
33	Rat (Fischer- 344)	8 wk (W)				16 (10/10 died)	Wanibuchi et al. 1996 DMA
34	Mouse (B6C3F1)	13 wk ad lib (F)				13.4 (1/10 males died; 1/10 females died)	NTP 1989b ROX
35	Pig	28 d (F)				5.70 (death in 2/18)	Edmonds and Baker 1986 ROX
Systemic							
36	Rat (Fischer- 344)	4 wk 5 d/wk 1x/d (G)	Renal			31 (papillary necrosis and hperplasia; cortical degeneration and necrosis)	Murai et al. 1993 DMA
			Bd Wt		31 (decreased body weight)		

Table 2-4. Levels of Significant Exposure to Organic Arsenic - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
37	Rat (Fischer- 344)	13 wk ad lib (F)	Resp	18.33 M 20.51 F			NTP 1989b ROX
			Cardio	18.33 M 20.51 F			
			Gastro	18.33 M 20.51 F			
			Hemato	9.11 M 10.25 F	18.23 M (pale 20.51 F skin)		
			Musc/skel	18.33 M 20.51 F			
			Hepatic	 10.25	1.14 M (incr relative liver wt.) 20.51 F		
			Renal		9.11 M (interstitial inflammation, focal regenerative hyperplasia of tubular cell epithelium and 10.25 F mineralization)	18.23 M (tubular necrosis) 20.51 F	
			Endocr	18.33 M 20.51 F			
			Dermal	18.33 M 20.51 F			
			Bd Wt	2.28 M 5.13 F	4.56 M (14% decreased body 10.25 F weight) (11% decreased body	9.11 M (26% decreased body 20.51 F weight) (33% decreased body	

Table 2-4. Levels of Significant Exposure to Organic Arsenic - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
38	Rat (Fischer- 344)	31 or 90 d ad lib (F)	Hemato	9.11 M 10.25 F			NTP 1989b ROX
			Hepatic	9.11 M 2.56 F	10.25 F (decrease relative liver weight)		
			Renal	2.28 M 10.25 F	9.11 M (increased relative kidney weight; mild tubular degeneration)		
39	Rat (Sprague-Dawley)	42 d (F)	Hemato	1.99 M			Siewicki 1981 DMA
			Hepatic	1.99 M			
			Renal	1.99 M			
			Bd Wt	1.99 M			
40	Mouse (B6C3F1)	13 wk ad lib (F)	Resp			38.7 (interstitial pneumonia)	NTP 1989b ROX
			Cardio	38.7			
			Gastro	38.7			
			Musc/skel	38.7			
			Hepatic	38.7			
			Renal	38.7			
			Endocr	38.7			
			Dermal	38.7			
			Bd Wt		38.7 (18% decreased body weight in males; 11% decreased body weight in females)		

Table 2-4. Levels of Significant Exposure to Organic Arsenic - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
41	Mouse (B6C3F1)	29 or 91 d ad lib (F)	Hemato	13.4			NTP 1989b ROX
			Hepatic	13.4			
			Renal	13.4			
42	Mouse (Swiss)	10 wk 1x/2d (GW)	Hemato	55			Prukop and Savage 1986 MMA
43	Rabbit (New Zealand)	40 d 1x/d (GW)	Gastro		2.3 M (intestinal hyperemia)		Jaghabir et al. 1989 MMA
			Hepatic		2.3 M (hepatocellular degeneration in 4/4)		
			Renal		2.3 M (interstitial nephritis in 2/4)		
Neurological							
44	Rat (Fischer- 344)	13 wk ad lib (F)		9.11 M		18.23 M (trembling, ataxia, hyperexcitability, slight inactivity, ruffled fur)	NTP 1989b ROX
				10.25 F		20.51 F	
45	Pig	28 d (F)		1.43		2.85 (muscle tremors)	Edmonds and Baker 1986 ROX
46	Pig	30 d (F)				0.87 (myelin degeneration)	Kennedy et al. 1986 ROX

Table 2-4. Levels of Significant Exposure to Organic Arsenic - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
47	Pig (Landrace)	30 d ad lib (F)				1.07 (seizures in 100%)	Rice et al. 1985 ROX
Reproductive							
48	Mouse (Swiss)	19 d 3 d/wk (GW)		5 M		55 M (reduced fertility)	Prukop and Savage 1986 MMA
Cancer							
49	Mouse A/J	50 wk ad lib (W)				5.5 M (CEL: lung tumors)	Hayashi et al. 1998 DMA

Table 2-4. Levels of Significant Exposure to Organic Arsenic - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
CHRONIC EXPOSURE							
Systemic							
50	Rat (Fischer- 344)	103 wk ad lib (F)	Resp	2.29 M 2.56 F			NTP 1989b ROX
			Cardio	2.29 M 2.56 F			
			Gastro	2.29 M 2.56 F			
			Musc/skel	2.29 M 2.56 F			
			Hepatic	2.29 M 2.56 F			
			Renal	2.29 M 2.56 F			
			Endocr	2.29 M 2.56 F			
			Dermal	2.29 M 2.56 F			
			Ocular	2.29 M 2.56 F			
			Bd Wt	2.29 M 2.56 F			
			Other	2.29 M 2.56 F			

Table 2-4. Levels of Significant Exposure to Organic Arsenic - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
51	Mouse (Fischer- 344)	103 wk ad lib (F)	Resp	9.7			NTP 1989b ROX
			Cardio	9.7			
			Gastro	9.7			
			Musc/skel	9.7			
			Hepatic	9.7			
			Renal	9.7			
			Endocr	9.7			
			Dermal	9.7			
			Ocular	9.7			
			Bd Wt	9.7 M	4.8 F (6-11% decr. body wt.)		

[a]The number corresponds to entries in Figure 2-4.

ad lib = ad libitum; Bd Wt = body weight; (C) = capsule; Cardio = cardiovascular; d = day(s); DMA = dimethyl arsinic acid or cacodylic acid; Endocr = endocrine; (F) = feed; F = female; Gastro = gastrointestinal; (GO) = gavage in oil; (GW) = gavage in water; Gd = gestation day; Hemato = hematological; IN = ingestion; LD50 = lethal dose, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; MMA = monomethylarsonic acid; MSMA = monosodium methane arsonate; Musc/skel = musculoskeletal; NOAEL = no-observable-adverse-effect level; Resp = respiratory; ROX = roxarsone; wk = week(s); x = time(s).

Figure 2-4. Levels of Significant Exposure to Organic Arsenic - Oral

Acute (≤14 days)

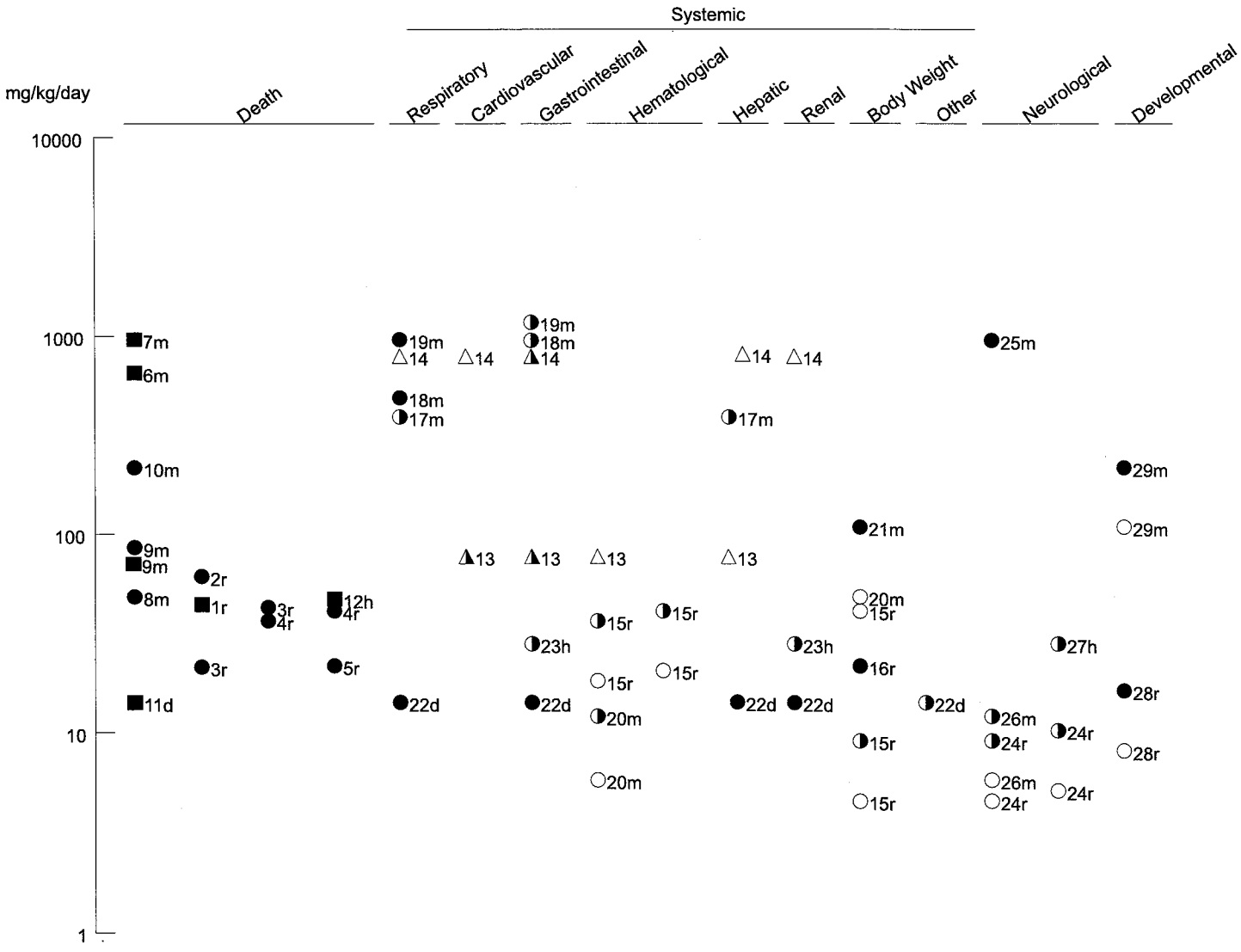


Figure 2-4. Levels of Significant Exposure to Organic Arsenic - Oral (*continued*)

Intermediate (15-364 days)

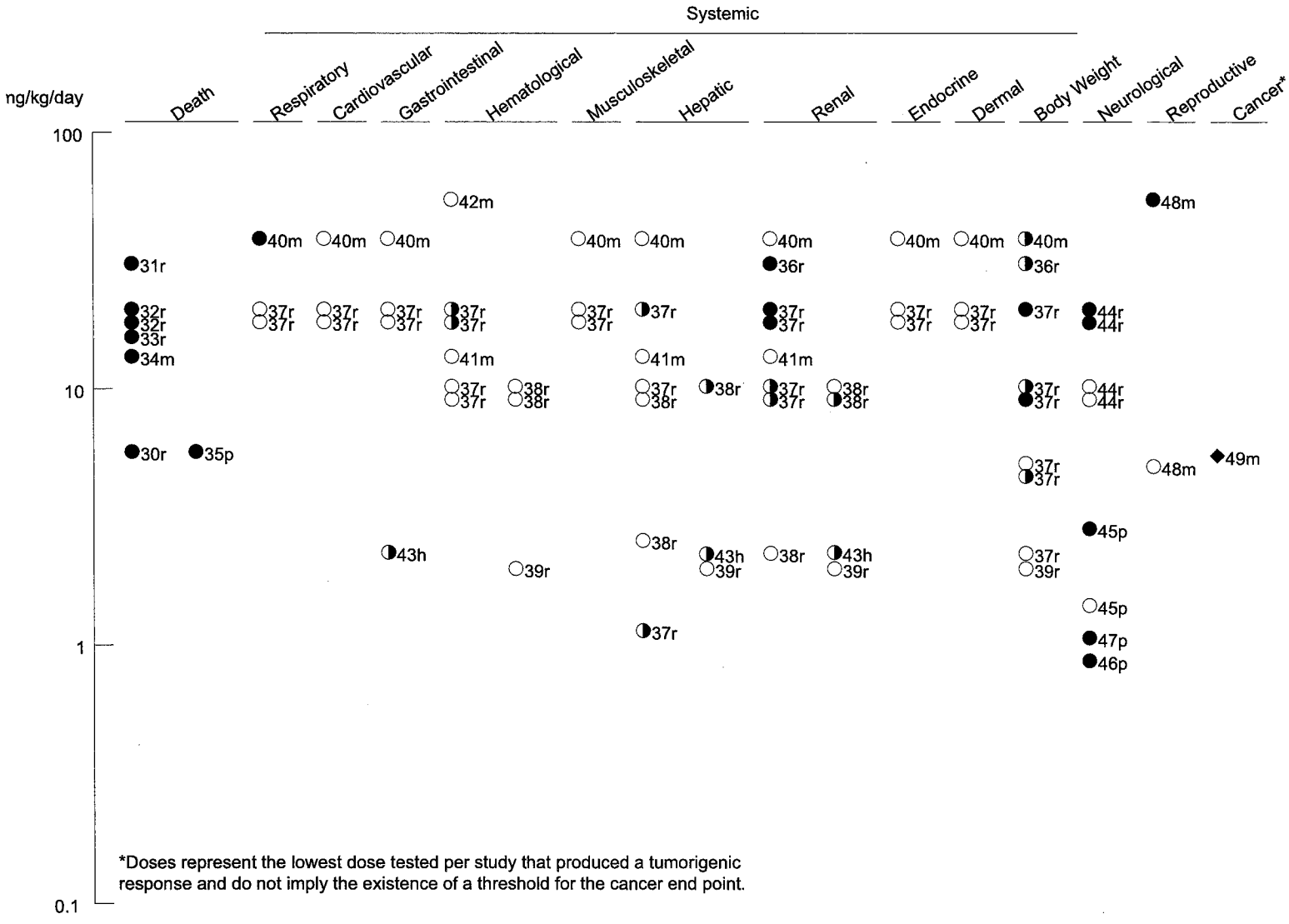
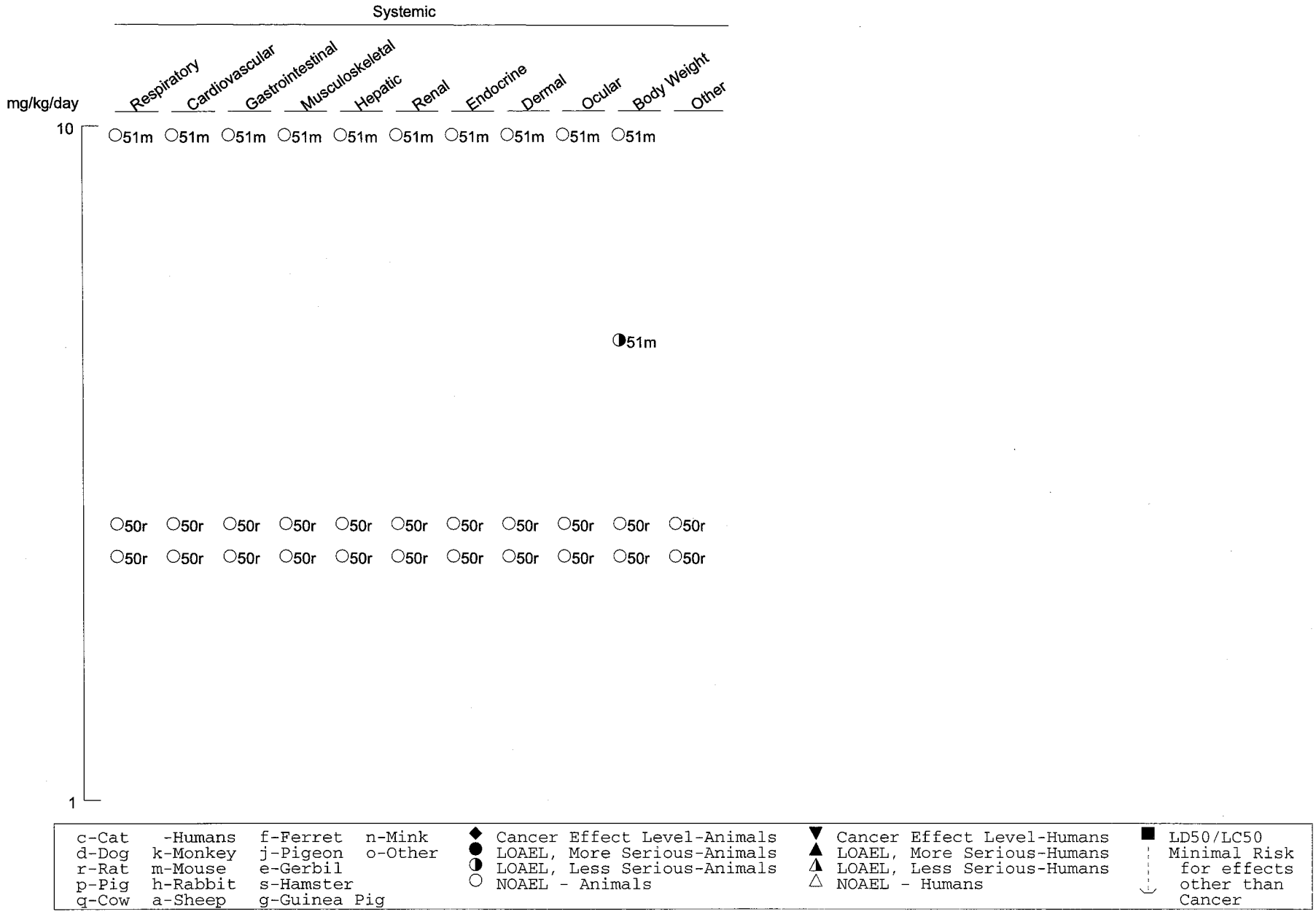


Figure 2-4. Levels of Significant Exposure to Organic Arsenic - Oral (continued)

Chronic (≥365 days)



22 to 121 mg As/kg in four cases where known amounts were ingested as a single bolus (Civantos et al. 1995; Hantson et al. 1996; Levin-Scherz et al. 1987; Quatrehomme et al. 1992). Two people in a family of eight died from ingestion of water containing about 110 ppm of arsenic for a week (Armstrong et al. 1984). This corresponded to a dose of about 2 mg As/kg/day. Based on a review of clinical reports in the older literature, Holland (1904) estimated the minimum lethal dose to be about 130 mg (also about 2 mg/kg). A similar estimate of 70–180 mg (about 1–3 mg/kg) was provided by Vallee et al. (1960). Death due to chronic arsenic exposure has been reported at lower concentrations. Five children between the ages of 2 and 7 years died from late sequelae of chronic arsenic poisoning after drinking contaminated water throughout their lives at estimated average doses of 0.05–0.1 mg As/kg/day (Zaldivar and Guillier 1977). A 22-year-old man with chronic arsenical dermatosis died from arsenic-related effects after lifetime exposure to an estimated average dose of 0.014 mg As/kg/day in the drinking water (Zaldivar et al. 1981). Systematic studies of lethality from chronic exposure attributable to increased risk of cardiovascular disease or cancer are discussed below in Sections 2.2.2.2 and 2.2.2.8, respectively.

Lethality studies in animals are consistent with the limited data in humans. Available LD_{50} values for arsenate and arsenite in rats and mice range from 15 to 175 mg As/kg (Dieke and Richter 1946; Gaines 1960; Harrisson et al. 1958; Kaise et al. 1985). The variability can be attributed to differences based on species, strain, specific route of exposure (feed vs. gavage), specific compound tested, and testing laboratory. Most deaths occurred within 1 day of exposure, but details regarding cause of death were not generally reported. Seven of 25 pregnant rats given a single gavage dose of 23 mg As/kg as arsenic trioxide on day 9 of gestation died soon after dosing, while no deaths occurred at doses of 4–15 mg As/kg (Stump et al. 1999). Data on lethality from repeated exposure studies in animals are relatively sparse. Seven of 20 pregnant rabbits died from repeated gavage doses of 1.5 mg As/kg/day as arsenic acid during gestation, while none died at 0.1-0.4 mg As/kg/day (Nemec et al. 1998). Chronic studies observed treatment-related mortality in monkeys exposed to 3 mg As/kg/day as arsenate (Heywood and Sortwell 1979), dogs exposed to 2.4 mg As/kg/day as arsenite or arsenate (Byron et al. 1967), mice exposed to 1 mg As/kg/day as arsenite (Schroeder and Balassa 1967), and rats exposed to 30 mg As/kg/day as lead arsenate (Kroes et al. 1974).

Reliable LOAEL and LD_{50} values for lethality from oral exposure to inorganic arsenicals in each species and duration category are recorded in Table 2-3 and plotted in Figure 2-3.

Organic Arsenicals. No studies were located regarding death in humans after oral exposure to organic arsenicals, but the acute lethality of MMA, DMA, and roxarsone have been investigated in several animal

studies. As shown in Table 2-4 and Figure 2-4, most acute lethal values range from about 15 to 70 mg As/kg (Jaghabir et al. 1988; Kerr et al. 1963; NTP 1989b; Rogers et al. 1981), although one study (Kaise et al. 1989) reported somewhat higher values (650–970 mg As/kg) for MMA and DMA in mice. The cause of death was not investigated in any of these studies. Intermediate-duration exposure to roxarsone caused death in pigs and rats at exposure levels of 5.7–21.5 mg As/kg/day (Edmonds and Baker 1986; Kerr et al. 1963; NTP 1989b). No increase in mortality was seen after chronic exposure of rats (2.3–2.6 mg/kg/day) or mice (9.7 mg/kg/day) to roxarsone (NTP 1989b).

2.2.2.2 Systemic Effects

The highest NOAEL values and all reliable LOAEL values for systemic effects from oral exposure in each species and duration category are recorded in Table 2-3 and plotted in Figure 2-3. Similar data for oral exposure to organic arsenicals are shown in Table 2-4 and plotted in Figure 2-4.

Respiratory Effects

Inorganic Arsenicals. Serious respiratory effects, including respiratory distress, hemorrhagic bronchitis, and pulmonary edema, have been reported in some cases of acute oral arsenic poisoning at doses of 8 mg As/kg and above (e.g., Civantos et al. 1995; Fincher and Koerker 1987; Levin-Scherz et al. 1987; Moore et al. 1994; Quatrehomme et al. 1992). These effects may be secondary to injury to the pulmonary vasculature (see Cardiovascular Effects, below). In addition, bronchitis and sequelae (bronchiectasis, bronchopneumonia) have been observed at autopsy in some chronic poisoning cases (Rosenberg 1974; Zaldivar 1974; Zaldivar and Guillier 1977). Bronchopneumonia secondary to arsenic-induced bronchitis was considered to be the cause of death in one young child who died after several years of exposure to an average dose of 0.08 mg As/kg/day (Zaldivar and Guillier 1977). In general, however, respiratory effects have not been widely associated with repeated oral ingestion of low arsenic doses. Nevertheless, a few studies have reported minor respiratory symptoms, such as cough, sputum, rhinorrhea, and sore throat, in people with repeated oral exposure to 0.03–0.05 mg As/kg/day (Ahmad et al. 1997; Mizuta et al. 1956).

There are few data regarding respiratory effects in animals following acute oral exposure to inorganic arsenic. An infant Rhesus monkey that died after 7 days of oral exposure to a complex arsenate salt at a dose of 3 mg As/kg/day exhibited bronchopneumonia with extensive pulmonary hemorrhage, edema, and necrosis (Heywood and Sortwell 1979). Two other monkeys in this treatment group survived a 1-year exposure period and had no gross or microscopic pulmonary lesions at sacrifice. Chronic oral studies in

dogs and rats treated with arsenate or arsenite also failed to find respiratory lesions (Byron et al. 1967; Kroes et al. 1974; Schroeder et al. 1968).

One study utilizing gallium arsenide included limited investigation of respiratory function. Respiration rate was significantly decreased in rats following ingestion of a single dose of gallium arsenide at 1,040 mg As/kg, but was unaffected at a dose of 520 mg As/kg (Flora et al. 1997a). Respiration rate was measured 1, 7, and 15 days after dosing, but the decrease was most noticeable after 15 days.

Organic Arsenicals. No respiratory effects were noted after acute human ingestion of 793 mg/kg arsenic (as monosodium methanearsenate) (Shum et al. 1995). Mice exhibited respiratory arrest after a single oral dose of 489 mg/kg DMA or 963 mg/kg MMA (Kaise et al. 1989), and lung ornithine decarboxylase activity was reduced after ingestion of one or two doses of 720 mg DMA/kg (Ahmad et al. 1999). Localized lung hemorrhage was observed in dogs after a single oral dose of 14.2 mg/kg roxarsone in a capsule (Kerr et al. 1963). No respiratory effects were seen after intermediate or chronic exposure of rats (18–20 or 2–3 mg/kg/day, respectively) or mice (39 or 10 mg/kg/day, respectively) to roxarsone (NTP 1989b).

Cardiovascular Effects

Inorganic Arsenicals. A number of studies in humans indicate that arsenic ingestion may lead to serious effects on the cardiovascular system. Characteristic effects on the heart from both acute and long-term exposure include altered myocardial depolarization (prolonged Q-T interval, nonspecific S-T segment changes) and cardiac arrhythmias (Cullen et al. 1995; Glazener et al. 1968; Goldsmith and From 1986; Heyman et al. 1956; Little et al. 1990; Mizuta et al. 1956; Moore et al. 1994). Hypertrophy of the ventricular wall was observed at autopsy after acute exposure to 93 mg As (Quatrehomme et al. 1992). Long-term low-level exposures may also lead to damage to the vascular system. The most dramatic example of this is "Blackfoot disease," a condition that is endemic in an area of Taiwan where average drinking water levels of arsenic range from 0.17 to 0.80 ppm (Tseng 1977), corresponding to doses of about 0.014–0.065 mg As/kg/day (Abernathy et al. 1989). The disease is characterized by a progressive loss of circulation in the hands and feet, leading ultimately to necrosis and gangrene (Chen et al. 1988b; Chi and Blackwell 1968; Tseng 1977, 1989; Tseng et al. 1968, 1995, 1996). Several researchers have presented evidence that other factors besides arsenic (e.g., other water contaminants, dietary deficits) may play a role in the etiology of this disease (Ko 1986; Lu et al. 1990; Yu et al. 1984). While this may be true, the clear association between the occurrence of Blackfoot disease and the intake of elevated arsenic

levels indicates that arsenic is at least a contributing factor. Arsenic exposure in Taiwan has also been associated with an increased incidence of cerebrovascular disease (Chiou et al. 1997) and ischemic heart disease (Chen et al. 1996; Hsueh et al. 1998b). Moreover, effects of arsenic on the vascular system have also been reported in a number of other populations. For example, increased arsenic exposure has been associated with an increase in hypertension in Bangladesh (Rahman et al. 1999). Studies in Chile indicate that ingestion of 0.6–0.8 ppm arsenic in drinking water (corresponding to doses of 0.02–0.06 mg As/kg/day, depending on age) increase the incidence of Raynaud's disease and of cyanosis of fingers and toes (Borgono and Greiber 1972; Zaldivar 1974, 1977; Zaldivar and Guillier 1977). Autopsy of five children from this region who died of apparent arsenic toxicity showed a marked thickening of small and medium sized arteries in tissues throughout the body, especially the heart (Rosenberg 1974). In addition, cardiac failure, arterial hypotension, myocardial necrosis, and thrombosis have been observed in children who died from chronic arsenic ingestion (Zaldivar 1974), as well as adults chronically exposed to arsenic (Dueñas et al. 1998). Likewise, thickening and vascular occlusion of blood vessels were noted in German vintners exposed to arsenical pesticides in wine and in adults who drank arsenic-contaminated drinking water (Roth 1957; Zaldivar and Guillier 1977). Some studies of chronic human arsenic exposure report no cardiovascular effects (Guha Mazumder et al. 1988; Silver and Wainman 1952; Valentine et al. 1992).

Similar alterations in vascular reactivity have been noted in rats given repeated oral doses of arsenic trioxide (11 mg As/kg/day) for several weeks (Bekemeier and Hirschelmann 1989), although no histological effects could be detected in the hearts of rats or dogs exposed to up to 30 mg As/kg/day as arsenate or arsenite for 2 years (Byron et al. 1967; Kroes et al. 1974; Schroeder et al. 1968). Acute exposure of rats to gallium arsenide at a dose of 1,040 mg As/kg resulted in an increase in blood pressure and heart rate, while 520 mg As/kg had no effect (Flora et al. 1997a).

Organic Arsenicals. No adverse cardiovascular effects were noted after acute human ingestion of 793 mg/kg arsenic (as monosodium methanearsenate) (Shum et al. 1995). However, sinus tachycardia was noted after acute ingestion of 77 mg/kg arsenic (as dimethyl arsenic acid and dimethyl arsenate) (Lee et al. 1995). No cardiovascular effects were seen after intermediate or chronic exposure of rats (18–20 or 2–3 mg/kg/day, respectively) or mice (39 or 10 mg/kg/day, respectively) to roxarsone (NTP 1989b).

Gastrointestinal Effects

Inorganic Arsenicals. Clinical signs of gastrointestinal irritation, including nausea, vomiting, diarrhea, and abdominal pain, are observed in essentially all cases of acute high-dose exposures to inorganic

arsenic (e.g., Armstrong et al. 1984; Campbell and Alvarez 1989; Cullen et al. 1995; Fincher and Koerker 1987; Goebel et al. 1990; Kingston et al. 1993; Levin-Scherz et al. 1987; Lugo et al. 1969; Moore et al. 1994). Similar signs are also frequently observed in groups or individuals with longer-term lower-dose exposures (e.g., Borgono and Greiber 1972; Cebrian et al. 1983; Franzblau and Lilis 1989; Guha Mazumder et al. 1988; Haupert et al. 1996; Holland 1904; Huang et al. 1985; Mizuta et al. 1956; Nagai et al. 1956b; Silver and Wainman 1952; Wagner et al. 1979; Zaldivar 1974), but effects are usually not detectable at exposure levels below about 0.01 mg As/kg/day (Harrington et al. 1978; Valentine et al. 1985). These symptoms generally decline within a short time after exposure ceases. Gastrointestinal irritation symptoms form the basis (in part) for the provisional acute oral MRL of 0.005 mg/kg/day for inorganic arsenic, as described in footnote b in Table 2-3. More severe symptoms (hematemesis, hemoperitoneum, gastrointestinal hemorrhage, and necrosis) have been reported in some cases with acute exposure to 8 mg As/kg or more (Civantos et al. 1995; Fincher and Koerker 1987; Levin-Scherz et al. 1987; Quatrehomme et al. 1992), and also in some people with long-term ingestion of 0.03–0.05 mg As/kg/day as a medicinal preparation (Lander et al. 1975; Morris et al. 1974). Clinical signs of gastrointestinal irritation were observed in monkeys and rats given repeated oral doses of arsenic (6 and 11 As/kg/day, respectively) for 2 weeks (Bekemeier and Hirschelmann 1989; Heywood and Sortwell 1979). Hemorrhagic gastrointestinal lesions have also been reported in animal studies. A monkey that died after repeated oral treatment with 6 mg As/kg/day for approximately one month was found to have acute inflammation and hemorrhage of the small intestine upon autopsy (Heywood and Sortwell 1979). This lesion was not found in other monkeys that died in this study, or in the survivors. Two pregnant mice that died after repeated gavage treatment with 24 mg As/kg/day as arsenic acid had hemorrhagic lesions in the stomach (Nemec et al. 1998). Gross gastrointestinal lesions (stomach adhesions, eroded luminal epithelium in the stomach) were seen frequently in rats treated by gavage with 8 mg As/kg/day as arsenic trioxide starting before mating and continuing through the end of gestation (Holson et al. 2000). The lesions were not found in rats treated with 4 mg As/kg/day in this study. No histological evidence of gastrointestinal injury was detected in rats exposed to arsenate or arsenite in the feed for 2 years at doses up to 30 mg As/kg/day, but dogs fed a diet containing 2.4 mg As/kg/day as arsenite for 2 years had some bleeding in the gut (Byron et al. 1967; Kroes et al. 1974).

Organic Arsenicals. Vomiting was noted after ingestion of 793 mg/kg arsenic (as monosodium methanearsenate) in a suicide attempt (Shum et al. 1995). Ingestion of 77 mg/kg arsenic (as dimethyl arsenic acid and dimethyl arsenate) induced vomiting, abdominal pain, hyperactive bowel, and diarrhea (Lee et al. 1995). Diarrhea and slight congestion of the intestines was observed in mice after a single dose of 954 mg/kg arsenic (as dimethylarsinic acid) or 1,177 mg/kg arsenic as MMA (Kaise et al. 1989).

Vomiting and gastrointestinal hemorrhage was observed in dogs after a single capsulized dose of 14 mg arsenic as roxarone (Kerr et al. 1963), although slightly higher doses administered for 13 weeks to rats and mice had no effect (NTP 1989b). One study in rabbits indicates that the intestinal wall may be irritated and weakened by repeated intake of MMA (Jaghabir et al. 1989), but this one observation is not enough to support a firm conclusion. No gastrointestinal effects were seen after chronic exposure of rats (2–3 mg/kg/day) or mice (10 mg/kg/day) to roxarsone (NTP 1989b)

Hematological Effects

Inorganic Arsenicals. Anemia and leukopenia are common effects of arsenic poisoning in humans, and have been reported following acute (Armstrong et al. 1984; Goldsmith and From 1986; Mizuta et al. 1956; Westhoff et al. 1975), intermediate (Franzblau and Lilis 1989; Heyman et al. 1956; Nagai et al. 1956b; Wagner et al. 1979), and chronic oral exposures (Glazener et al. 1968; Guha Mazumder et al. 1988; Kyle and Pease 1965; Tay and Seah 1975) at doses of 0.05 mg As/kg/day or more. These effects may be due to both a direct cytotoxic or hemolytic effect on the blood cells (Armstrong et al. 1984; Fincher and Koerker 1987; Goldsmith and From 1986; Kyle and Pease 1965; Lerman et al. 1980) and a suppression of erythropoiesis (Kyle and Pease 1965; Lerman et al. 1980). However, hematological effects are not observed in all cases of arsenic exposure (Harrington et al. 1978; Huang et al. 1985; Silver and Wainman 1952; Southwick et al. 1981) or even all acute poisoning cases (Cullen et al. 1995; Moore et al. 1994).

In an acute animal study, Tice et al. (1997) found that there was a decrease in polychromatic erythrocytes in the bone marrow of mice treated with 6 mg As/kg/day for 1 or 4 days. There was no effect at 3 mg As/kg/day. Long-term studies in dogs found mild anemia in dogs fed arsenite or arsenate for 2 years at 2.4 mg As/kg/day, but no hematological effect in dogs fed 1 mg As/kg/day for 2 years or 1.9 mg As/kg/day for 26 weeks (Byron et al. 1967; Neiger and Osweiler 1989). Chronic rat studies found little or no evidence of anemia at doses up to 30 mg As/kg/day, even with co-exposure to lead (Byron et al. 1967; Kroes et al. 1974). No hematological effects were found in monkeys exposed to arsenic doses of 3–6 mg As/kg/day for 1 year (Heywood and Sortwell 1979).

Rats exposed to arsenate for 6 weeks had decreased activities of several enzymes involved in heme synthesis, but data were not provided on whether this resulted in anemia (Woods and Fowler 1977, 1978). Gallium arsenide also disrupts heme synthesis in rats, although the evidence suggests that this effect of this compound is due primarily to the gallium moiety (Flora et al. 1997a).

Organic Arsenicals. No adverse hematological effects were noted for a man who ingested 77 mg/kg As (as dimethyl arsenic acid and dimethyl arsenate) (Lee et al. 1995). Several studies in rats and mice have not detected any significant hematological effects from repeated exposure (2–13 weeks) to MMA (Prukop and Savage 1986), DMA (Siewicki 1981), or roxarsone (NTP 1989b) at doses of 5–55 mg As/kg/day. These data suggest that oral exposure to organic arsenicals is unlikely to cause hematological effects, but this is not certain.

Musculoskeletal Effects

Inorganic Arsenicals. No studies were located regarding musculoskeletal effects in humans or animals after oral exposure to inorganic arsenicals.

Organic Arsenicals. No studies were located regarding musculoskeletal effects in humans after oral exposure to organic arsenicals. No musculoskeletal effects were seen after intermediate or chronic exposure of rats (18–20 or 2–3 mg/kg/day, respectively) or mice (39 or 10 mg/kg/day, respectively) to roxarsone (NTP 1989b)

Hepatic Effects

Inorganic Arsenicals. A number of studies in humans exposed to inorganic arsenic by the oral route have noted signs or symptoms of hepatic injury. Clinical examination often reveals that the liver is swollen and tender (Chakraborty and Saha 1987; Franklin et al. 1950; Guha Mazumder et al. 1988; Mizuta et al. 1956; Silver and Wainman 1952; Wade and Frazer 1953; Zaldivar 1974), and analysis of blood sometimes shows elevated levels of hepatic enzymes (Armstrong et al. 1984; Franzblau and Lilis 1989; Hernandez-Zavala et al. 1998). These effects are most often observed after repeated exposure to doses of 0.01–0.1 mg As/kg/day (Chakraborty and Saha 1987; Franklin et al. 1950; Franzblau and Lilis 1989; Guha Mazumder et al. 1988; Mizuta et al.1956; Silver and Wainman 1952; Wade and Frazer 1953), although doses as low as 0.006 mg As/kg/day have been reported to be effective with chronic exposure (Hernandez-Zavala et al. 1998). Hepatic effects have also been reported in acute bolus poisoning cases at doses of 2 mg As/kg/day or more (Hantson et al. 1996; Kamijo et al. 1998; Levin-Scherz et al. 1987; Quatrehomme et al. 1992), although acute exposure to 19 mg As/kg did not cause hepatic effects in an infant (Cullen et al. 1995). Histological examination of the livers of persons chronically exposed to similar doses has revealed a consistent finding of portal tract fibrosis (Guha Mazumder et al. 1988; Morris et al. 1974; Piontek et al. 1989; Szuler et al. 1979), leading in some cases to portal hypertension and

bleeding from esophageal varices (Szuler et al. 1979). Several researchers consider that these hepatic effects are secondary to damage to the hepatic blood vessels (Morris et al. 1974; Rosenberg 1974), but this is not directly established.

Acute exposure of monkeys to 6 mg As/kg/day resulted in vacuolization of the hepatocytes (Heywood and Sortwell 1979). Studies in dogs or mice have not detected clinically significant hepatic injury following exposure to either arsenite or arsenate (Byron et al. 1967; Fowler and Woods 1979; Kerkvliet et al. 1980; Neiger and Osweiler 1989; Schroeder and Balassa 1967), although enlargement of the common bile duct was noted in rats fed either arsenate or arsenite in the diet for 2 years (Byron et al. 1967; Kroes et al. 1974) and lipid vacuolation and fibrosis were seen in the liver of rats exposed to 12 mg As/kg/day as arsenate in the drinking water for 6 weeks (Fowler et al. 1977). Increases in liver zinc and copper concentrations were noted in rats receiving a single oral dose of 10 mg As/kg as sodium arsenite (Flora and Tripathi 1998) and hepatic levels of malondialdehyde were increased and glutathione levels were decreased in livers of rats receiving 200 mg As/kg as GaAs (Flora et al. 1998). Elevated levels of serum aspartate aminotransferase (AST) were observed in rats administered a single oral dose of 100 mg As/kg as GaAs (Flora et al. 1998).

Organic Arsenicals. No adverse hepatic effects were noted after ingestion of 793 mg/kg arsenic (as monosodium methanearsenate) or 77 mg/kg arsenic (as dimethyl arsenic acid and dimethyl arsenate) in a suicide attempt (Lee et al. 1995; Shum et al. 1995). Generalized icterus was reported in dogs after acute exposure to roxarsone (Kerr et al. 1963). Some small fluctuations in liver weight have been noted in rats and mice after intermediate oral exposure to roxarsone, but the toxicological significance of this is not clear and is not observed after chronic exposure of rats and mice to lower doses (NTP 1989b). Histological examination of liver from rabbits given repeated oral doses of MMA showed diffuse inflammation and hepatocellular degeneration (Jaghabir et al. 1989), but the lesions were not severe. No effects were observed in rats exposed to DMA (Siewicki 1981), but mice exposed to one or two oral doses of 720 mg DMA/kg had decreased liver glutathione and cytochrome P-450 content and serum ornithine decarboxylase activity (Ahmad et al. 1999). These data suggest that organic arsenicals may cause mild injury to the liver, but the data are too limited to draw firm conclusions.

Renal Effects

Inorganic Arsenicals. Most case studies of acute and chronic arsenic toxicity do not report clinical signs of significant renal injury, even when other systems are severely impaired (e.g., Cullen et al. 1995;

Franzblau and Lilis 1989; Jenkins 1966; Kersjes et al. 1987; Mizuta et al. 1956; Silver and Wainman 1952). In some cases, elevated serum levels of creatinine or bilirubin have been noted (Armstrong et al. 1984; Levin-Scherz et al. 1987; Moore et al. 1994), and mild proteinuria may occur (Armstrong et al. 1984; Glazener et al. 1968; Tay and Seah 1975). Acute renal failure in some bolus poisoning episodes (e.g., Fincher and Koerker 1987; Goebel et al. 1990; Levin-Scherz et al. 1987; Lugo et al. 1969; Moore et al. 1994) is probably a result of fluid imbalances or vascular injury (Rosenberg 1974; Zaldivar 1974). Glomerular congestion has been observed after an acute exposure to high doses (Quatrehomme et al. 1992). Studies in animals also indicate that the kidney is not a major target organ for inorganic arsenic (Byron et al. 1967; Schroeder and Balassa 1967; Woods and Southern 1989), although some mild histological changes in renal tubules of monkeys exposed to arsenate for 2 weeks was noted by Heywood and Sortwell (1979), and some mild alterations in renal mitochondria in rats exposed to arsenate for 6 weeks were noted by Brown et al. (1976). Mild proteinuria (Flora et al. 1998) and an increase in kidney zinc concentration (Flora and Tripathi 1998) have also been noted in rats exposed orally to a single dose of 100 mg As/kg as GaAs or 10 mg As/kg as sodium arsenite, respectively. These data suggest that the kidney is relatively less sensitive to arsenic than most other organ systems, and renal effects are unlikely to be of concern except secondary to fluid imbalances or cardiovascular injury.

Organic Arsenicals. No adverse renal effects were noted after ingestion of 793 mg/kg arsenic (as monosodium methanearsenate) in a suicide attempt (Shum et al. 1995). Hematuria and congested kidneys have been observed in dogs after acute exposure, and tubular degeneration and necrosis have been noted in rats (but not mice) given repeated oral doses of roxarsone (up to 20 mg/kg/day As) (Abdo et al. 1989; Kerr et al. 1963; NTP 1989b). Oligouria was noted after acute exposure and interstitial nephritis and tubular nephrosis have been noted in rabbits given repeated oral doses of MMA (Jaghabir et al. 1989). However, no renal injury was observed in rats and mice chronically exposed to roxarsone at lower doses (2–10 mg/kg/day As) (NTP 1989b). These data suggest that organic arsenicals can lead to significant renal injury, although the minimal dose is not well defined.

Endocrine Effects

Inorganic Arsenicals. Very little has been written about the effects of oral exposure to arsenic on endocrine glands. In a report of the autopsy of five children who died in Chile after chronic exposure to arsenic in the drinking water, arterial thickening in pancreas was noted (Rosenberg 1974). An association has been demonstrated between exposure to arsenic in drinking water and increased incidence of diabetes

mellitus in Bangladesh (Rahman et al. 1998). No studies in animals were found in which effects of oral exposure to inorganic arsenic on endocrine organs were described.

Organic Arsenicals. No studies of effects of organic arsenic compounds on human endocrine glands were found. No adverse effects were seen in the adrenal or pituitary glands, thyroid, or pancreas after intermediate or chronic exposure of rats (18–20 or 2–3 mg/kg/day, respectively) or mice (39 or 10 mg/kg/day, respectively) to roxarsone (NTP 1989b).

Dermal Effects

Inorganic Arsenicals. One of the most common and characteristic effects of arsenic ingestion is a pattern of skin changes that include generalized hyperkeratosis and formation of hyperkeratotic warts or corns on the palms and soles, along with areas of hyperpigmentation interspersed with small areas of hypopigmentation on the face, neck, and back. These and other dermal effects have been noted in a large majority of human studies involving repeated oral exposure (e.g., Ahmad et al. 1997; Bickley and Papa 1989; Borgono and Greiber 1972; Borgono et al. 1980; Cebrian et al. 1983; Chakraborty and Saha 1987; Foy et al. 1992; Franklin et al. 1950; Franzblau and Lilis 1989; Guha Mazumder et al. 1988, 1998a, 1998c; Haupert et al. 1996; Huang et al. 1985; Lander et al. 1975; Luchtrath 1983; Mizuta et al. 1956; Morris et al. 1974; Nagai et al. 1956b; Piontek et al. 1989; Rosenberg 1974; Saha and Poddar 1986; Silver and Wainman 1952; Szuler et al. 1979; Tay and Seah 1975; Tseng et al. 1968; Wade and Frazer 1953; Wagner et al. 1979; Wong et al. 1998a, 1998b; Zaldivar 1974, 1977). In cases of low-level chronic exposure (usually from water), these skin lesions appear to be the most sensitive indication of effect, so this end point is considered to be the most appropriate basis for establishing a chronic oral MRL. This is supported by the finding that other effects (hepatic injury, vascular disease, neurological effects) also appear to have similar thresholds. As shown in Table 2-3 and Figure 2-3, numerous studies in humans have reported dermal effects at chronic dose levels ranging from about 0.01 to 0.1 mg As/kg/day (Bickley and Papa 1989; Borgono and Greiber 1972; Borgono et al. 1980; Cebrian et al. 1983; Chakraborty and Saha 1987; Foy et al. 1992; Franklin et al. 1950; Guha Mazumder et al. 1988; Huang et al. 1985; Luchtrath 1983; Piontek et al. 1989; Silver and Wainman 1952; Tseng et al. 1968; Zaldivar 1974, 1977). Several epidemiological studies of moderately sized populations (20–200 people) exposed to arsenic through drinking water have detected no dermal or other effects at average chronic doses of 0.0004–0.01 mg As/kg/day (Cebrian et al. 1983; Guha Mazumder et al. 1988; Harrington et al. 1978; Southwick et al. 1981; Valentine et al. 1985), and one very large study (based on 17,000 people) detected no effects in any person at an average total daily intake (from water plus food) of 0.0008 mg As/kg/day

(Tseng et al. 1968). This value has been used to calculate a chronic oral MRL for inorganic arsenic of 0.0003 mg/kg/day, as described in footnote c in Table 2-3.

Another prominent dermal effect associated with chronic ingestion of inorganic arsenic is skin cancer. As discussed in greater detail in Section 2.2.2.8 (below), some of these skin cancers may evolve from the hyperkeratotic corns or warts, while the areas of altered pigmentation are not considered to be precancerous (EPA 1988e).

Dermal lesions similar to those observed in humans have not been noted in oral exposure studies in monkeys (Heywood and Sortwell 1979), dogs (Byron et al. 1967), or rodents (Schroeder et al. 1968).

Organic Arsenicals. No studies were located regarding dermal effects in humans or animals after oral exposure to organic arsenicals.

Ocular Effects

Inorganic Arsenicals. Periorbital swelling was reported in people drinking contaminated well water at an approximate dose of 0.2 mg As/kg for 1 week (Armstrong et al. 1984). Facial edema, generally involving the eyelids, was a prominent feature of arsenic poisoning among 220 cases associated with an episode of arsenic contamination of soy sauce in Japan (Mizuta et al. 1956). Exposure was to an estimated dose of 0.05 mg/kg/day and lasted for up to 2–3 weeks. The edema developed soon after the initial exposure and then subsided. This effect forms the basis (in part) for the provisional acute oral MRL of 0.005 mg/kg/day for inorganic arsenic, as described in footnote b in Table 2-3. Nemec et al. (1998) noted the appearance of dried red material around the eyes of mice receiving daily oral doses of 24 mg As/kg as arsenic acid for 10 days during gestation.

Organic Arsenicals. No studies were located regarding ocular effects in humans or animals after oral exposure to organic arsenicals.

Body Weight Effects

Inorganic Arsenicals. A 41-year old woman exposed to arsenic in the drinking water for 4 months at an approximate dose of 0.06 mg As/kg/day reported losing 40 pounds (18 kg) of body weight before seeking treatment (Wagner et al. 1979). Weight loss was also among the effects observed in a series of

475 chronic arsenism patients hospitalized in Antofagasto, Chile after receiving approximate doses of 0.02 mg As/kg/day in the drinking water for an unspecified number of years (Zaldivar 1974).

Reductions in body weight gain are commonly seen in animal studies of ingested arsenic. In pregnant rats, body weight gain was reduced by gavage treatment with 23 mg As/kg/day as arsenic trioxide on day 9 of gestation (NOAEL=15 mg As/kg/day, Stump et al. 1999), and by repeated gavage treatment with 8 mg As/kg/day as arsenic trioxide from 2 weeks prior to mating through gestation (NOAEL=4 mg As/kg/day, Holson et al. 2000). In 6-week rat studies, body weight gain was decreased at 11–12 mg As/kg/day, but not at 6–9 mg As/kg/day (Brown et al. 1976; Fowler et al. 1977). In chronic rat studies of arsenate and arsenite, body growth decreases were found at doses as low as 2 mg As/kg/day in feeding studies (Byron et al. 1967; Kroes et al. 1974), while rats exposed to lower levels of sodium arsenite in the drinking water (0.6 mg As/kg/day) throughout their lifetimes grew normally (Schroeder et al. 1968). Rats given a single oral dose of 100 mg As/kg as GaAs exhibited a 15% reduction in body weight compared to controls 7 days after exposure (Flora et al. 1998). Body weight gain was decreased in mice at 24 mg As/kg/day in a gestation exposure study (Nemec et al. 1998), 10 mg As/kg/day in a 6-week study (Fowler and Woods 1979), and 1 mg As/kg/day in a 2-year study (Schroeder and Balassa 1967). Growth was unaffected in mice that received 12 mg As/kg/day in the gestation exposure study (Nemec et al. 1998), 5 mg As/kg/day in the 6-week study (Fowler and Woods 1979), or 0.7–0.8 mg As/kg/day in 1–3 month arsenate drinking water studies (Healy et al. 1998). Dogs chronically treated with 2.4 mg As/kg/day as sodium arsenite lost 44–61% of their starting body weight and died, while lower doses had no effect on growth (Byron et al. 1967). Weight depression was also reported in dogs chronically treated with 2.4 mg As/kg/day as sodium arsenate (Byron et al. 1967). Feed consumption and body weight gain were significantly reduced in a dose-related manner in dogs fed 1.5 or 1.9 mg As/kg/day as sodium arsenite in the diet (Neiger and Osweiler 1989). Dogs in the high-dose group lost 25% of their body weight over the 17-week study period. Pair-fed controls lost weight at the same rate as high-dose dogs, showing that the effect on body weight was due to reduced feed consumption, rather than a direct effect of arsenic.

Organic Arsenicals. No studies were located regarding body weight effects in humans after oral exposure to organic arsenicals. In animal studies of organic arsenicals, decreases in body weight gain were observed in rats and mice after acute, intermediate, and chronic duration exposure to DMA and roxarsone (Murai et al. 1993; NTP 1989b; Rogers et al. 1981; Siewicki 1981). The lowest dose to produce a decrease in growth was approximately 4 mg As/kg/day (NTP 1989b).

2.2.2.3 Immunological and Lymphoreticular Effects

Inorganic Arsenicals. No studies were located regarding immunological and lymphoreticular effects in humans after oral exposure to inorganic arsenicals. No evidence of immunosuppression was detected in mice exposed to arsenate at levels up to 100 ppm (20 mg As/kg/day) in drinking water (Kerkvliet et al. 1980). This NOAEL is shown in Table 2-3 and Figure 2-3. Gallium arsenide at doses of 52–260 mg As/kg/day produced significant, dose-related decreases in relative spleen weight, spleen cellularity, humoral immune response (antibody forming cell response to sheep RBC), and delayed type hypersensitivity in rats (Flora et al. 1998). However, it is not clear to what extent these effects are due to the arsenic moiety.

Organic Arsenicals. No studies were located regarding immunological and lymphoreticular effects in humans or animals after oral exposure to organic arsenicals.

2.2.2.4 Neurological Effects

Inorganic Arsenicals. A large number of epidemiological studies and case reports indicate that ingestion of inorganic arsenic can cause injury to the nervous system. Acute, high-dose exposures (2 mg As/kg/day or above) often lead to encephalopathy, with signs and symptoms such as headache, lethargy, mental confusion, hallucination, seizures, and coma (Armstrong et al. 1984; Civantos et al. 1995; Cullen et al. 1995; Danan et al. 1984; Fincher and Koerker 1987; Levin-Scherz et al. 1987; Quatrehomme et al. 1992). Repeated exposures to lower levels (0.03–0.1 mg As/kg/day) are typically characterized by a symmetrical peripheral neuropathy (Foy et al. 1992; Franzblau and Lilis 1989; Guha Mazumder et al. 1988; Hindmarsh et al. 1977; Huang et al. 1985; Mizuta et al. 1956; Silver and Wainman 1952; Szuler et al. 1979; Wagner et al. 1979). This neuropathy usually begins as a numbness in the hands and feet, but later may develop into a painful "pins and needles" sensation. Both sensory and motor nerves are affected, and muscle weakness often develops, sometimes leading to wrist-drop or ankle-drop (Chhuttani et al. 1967; Heyman et al. 1956). Diminished sensitivity to stimulation and abnormal patellar reflexes have also been reported (Mizuta et al. 1956). Histological examination of nerves from affected individuals reveals a dying-back axonopathy with demyelination (Goebel et al. 1990; Hindmarsh and McCurdy 1986). Some recovery may occur following cessation of exposure, but this is a slow process and recovery is usually incomplete (Fincher and Koerker 1987; LeQuesne and McLeod 1977; Murphy et al. 1981). Peripheral neuropathy is also sometimes seen following acute high-dose exposures, with or without the previously described encephalopathy (Armstrong et al. 1984; Fincher and Koerker 1987; Goebel et al. 1990; Hantson

et al. 1996; Kamijo et al. 1998). Neurological effects were not generally found in populations chronically exposed to doses of 0.006 mg As/kg/day or less (Harrington et al. 1978; Hindmarsh et al. 1977; Southwick et al. 1981), although fatigue, headache, dizziness, insomnia, nightmare, and numbness of the extremities were among the symptoms reported at 0.005, but not 0.004 mg As/kg/day in a study of 31,141 inhabitants of 77 villages in Xinjiang, China (Lianfang and Jianzhong 1994). Among animals, neurological effects have been observed only in monkeys and rabbits. Heywood and Sortwell (1979) remarked salivation and uncontrolled head shaking in two monkeys given several doses of 6 mg As/kg/day as arsenate, while no such effects were noted in monkeys given 3 mg As/kg/day for 2 weeks. Nemec et al. (1998) observed ataxia and prostration in pregnant female rabbits treated with 1.5 mg As/kg/day repeatedly during gestation, but not in rabbits treated with 0.4 mg As/kg/day.

The highest NOAEL values and all reliable LOAEL values for neurological effects from inorganic arsenic in each species and duration category are recorded in Table 2-3 and plotted in Figure 2-3.

Organic Arsenicals. One case report of the ingestion of organic arsenic was located. A 52-year-old Vietnamese woman ingested an unspecified amount of organic arsenic in the form of bird's nest soup, resulting in numbness and tingling of the fingertips, toes, and circumoral region. Discontinuation of exposure resulted in the disappearance of symptoms (Luong and Nguyen 1999). Several studies in pigs indicate that repeated oral doses of roxarsone (0.87–5.8 mg As/kg/day for 1 month) can cause significant neurotoxicity (Edmonds and Baker 1986; Rice et al. 1985). The main signs were muscle tremors, partial paralysis, and seizures. Histological examinations of the spinal cord revealed a time-dependent degeneration of myelin and axons (Kennedy et al. 1986). Such prominent signs of neurological effects were not detected in rats or mice exposed to roxarsone, although evidence of neurological effects (hyperexcitability, ataxia, trembling) was noted in rats at the highest dose (11.4 mg As/kg/day) (NTP 1989b). These data (shown in Table 2-4 and Figure 2-4) suggest that organic arsenicals (at least the phenyl arsenates) are neurotoxic at high doses.

2.2.2.5 Reproductive Effects

Inorganic Arsenicals. Only one study was located relevant to reproductive effects in humans after oral exposure to inorganic arsenicals. Lugo et al. (1969) reported a case of a 17-year-old mother who ingested inorganic arsenic (Cowley's Rat and Mouse Poison) at 30-week pregnancy. She was admitted for treatment of acute renal failure 24 hours after she ingested approximately 30 mL of arsenic trioxide (0.39 mg As/kg). She went into labor and delivered a live female infant weighing 2 pounds, 7 ounces

with a 1-minute Apgar score of 4. The infant's clinical condition deteriorated and she died at 11 hours of age.

Reproductive performance was not affected in female rats that received gavage doses of 8 mg As/kg/day (as As_2O_3) from 14 days prior to mating through gestation day 19 (Holson et al. 2000). Reproductive indices that were evaluated included the precoital interval (time to mating), mating index (percentage of rats mated), and fertility index (percentage of matings resulting in pregnancy). In a 3-generation study in mice given sodium arsenite in drinking water at an average dose of 1 mg As/kg/day, there was a significant increase in the incidence of small litters and a trend toward decreased number of pups per litter in all three generations of the treated group (Schroeder and Mitchner 1971). This finding is consistent with the results of developmental toxicity studies reported in Section 2.2.2.6. NOAEL and LOAEL values from these studies are show in Table 2-3 and Figure 2-3.

Organic Arsenicals. No studies were located regarding reproductive effects in humans after oral exposure to organic arsenicals. Male and female mice dosed with MMA (55 mg As/kg/day) prior to mating and during pregnancy produced fewer litters than normal, an effect that was attributable mainly to decreased fertility of the males (Prukop and Savage 1986). This observation (shown in Figure 2-4 and summarized in Table 2-4) suggests that spermatogenesis or sperm function might be impaired by organic arsenicals, but this was not studied directly.

2.2.2.6 Developmental Effects

Inorganic Arsenicals. Whether ingestion of inorganic arsenic may cause developmental effects in humans has not been extensively investigated. Lugo et al. (1969) reported a case of a mother who ingested inorganic arsenic (Cowley's Rat and Mouse Poison) at 30 weeks of gestation. She went into labor and delivered a live female infant weighing 2 pounds, 7 ounces with a 1-minute Apgar score of 4. The infant's clinical condition deteriorated with frequent episodes of apnea and bradycardia; subsequent venous blood gas determinations documented hypoxia, hypercapnea, and acidosis. The infant died at 11 hours of age. Autopsy performed 8 hours after death showed organ immaturity, generalized petechial hemorrhages, and hyaline membrane disease. Severe intra-alveolar pulmonary hemorrhage was remarkable. High arsenic levels were found in the infant’s liver, kidney, and brain, demonstrating easy passage of inorganic arsenic across the placenta. The authors considered most of the findings in the neonate to be attributable to immaturity, but suggested that arsenic may have played a role in the severe intra-alveolar hemorrhaging that contributed to death.

No overall association between arsenic in drinking water and congenital heart defects was detected in a case-control study in Boston (Zierler et al. 1988), although an association with one specific lesion (coarctation of the aorta) was noted (odds ratio [OR]=3.4, 95% CI=1.3–8.9). Due to the small study size (a total of 270 cases with any congenital heart disease and 665 controls), this association could be due to random variation. In a similar case-control study, a marginal association (not statistically significant) was noted between detectable levels of arsenic in drinking water and the occurrence of spontaneous abortion (Aschengrau et al. 1989). Marginal positive associations were also noted for mercury, potassium, silica, and water hardness in this study, while a decreased incidence of abortion was associated with sulfate, nitrate, and alkalinity. This pattern of divergent associations for multiple contaminants suggests that at least some of the apparent associations may be random, or may be due to covariation with other risk factors. Thus, neither of these studies provides convincing evidence that ingestion of arsenic, at least at the levels usually encountered in drinking water, causes developmental toxicity in humans.

Studies in animals, however, suggest that ingested inorganic arsenic may produce developmental effects at high doses that also produce overt maternal toxicity. Rats treated with a single gavage dose of 23 mg As/kg as arsenic trioxide on day 9 of gestation had a significant increase in post-implantation loss and a decrease in viable fetuses per litter, while those treated with 15 mg As/kg showed no effects (Stump et al. 1999). Rats treated by daily gavage with 8 mg As/kg/day starting 14 days before mating and continuing through gestation had significantly reduced fetal body weights and significantly increased incidences of several skeletal variations (unossified sternebrae #5 or #6, slight or moderate sternebrae malalignment, 7th cervical ribs) that the researchers considered to be consequences of developmental growth retardation (Holson et al. 2000). No developmental effects were found at 4 mg As/kg/day in this study. Studies in mice found increased fetal mortality, decreased fetal body weight, a low incidence of gross malformations (primarily exencephaly), and an increase in skeletal malformations in mice given single gavage doses of 23–48 mg As/kg during gestation (Baxley et al. 1981; Hood et al. 1978), with no effects at 11 mg As/kg. Similarly, in mice treated with 24 mg As/kg/day as arsenic acid on days 6–15 of gestation, there was a significant increase in the number of resorptions per litter (42 vs 4% in controls) and significant decreases in the number of live pups per litter (6.6 vs 12.3 in controls) and mean fetal weight (1.0 g vs 1.3 g in controls), while no developmental effects were found at 12 mg As/kg/day (Nemec et al. 1998). Hamsters treated with a single gavage dose of 14 mg As/kg during gestation also had increased fetal mortality and decreased fetal body weight (Hood and Harrison 1982), with no effect at 11 mg As/kg. However, the most sensitive species was the rabbit, which had increased resorptions and decreased viable fetuses per litter at 1.5 mg As/kg/day and a developmental NOAEL of 0.4 mg As/kg/day, following repeated gavage dosing with arsenic acid during gestation (Nemec et al. 1998). In each of these studies (except Hood et al.

1978, which failed to report maternal effects), overt maternal toxicity, including death in some cases, was found at the same or lower doses as the developmental effects (Baxley et al. 1981; Holson et al. 2000; Hood and Harrison 1982; Nemec et al. 1998; Stump et al. 1999).

It is noteworthy that the effect in the 3-generation reproduction study in mice by Schroeder and Mitchner (1971), decreased pups per litter (all generations), is consistent with the findings of many of these shorter-term studies (Baxley et al. 1981; Hood and Harrison 1982; Hood et al. 1978; Nemec et al. 1998; Stump et al. 1999). The dose in this long-term study was 1 mg As/kg/day; in a 2-year study by these researchers, this dose produced effects such as decreased body weight gain and increased mortality (Schroeder and Balassa 1967).

These studies (shown in Table 2-3 and Figure 2-3) indicate that the fetus may be affected by ingested arsenic, but suggest that the fetus is not more susceptible to arsenic than the mother.

Organic Arsenicals. No studies were located regarding developmental effects in humans after oral exposure to organic arsenicals. However, effects on fetal development (malformed palate, reduced fetal weight, delayed ossification, increased fetal mortality) have been observed in rats and mice given repeated oral doses of DMA during gestation (Rogers et al. 1981). These findings (summarized in Table 2-4 and shown Figure 2-4) suggest that high doses of organic arsenicals may have significant developmental toxicity, but the data are too limited to draw broad conclusions.

2.2.2.7 Genotoxic Effects

Inorganic Arsenicals. Investigations of genotoxic effects of ingested arsenic have yielded mixed results. A study of p53 mutations in arsenic-related skin cancers from patients in Taiwan exposed to arsenic from drinking water found a high rate of p53 mutations and different types of p53 mutations compared with those seen in UV-induced skin cancers (Hsu et al. 1999). In humans exposed to Fowler's solution (potassium arsenite, usually taken at a dose of about 0.3 mg As/kg/day [Holland 1904]), increased sister chromatid exchange, but no increase in chromosomal aberrations, was reported in one study (Burgdorf et al. 1977), while just the converse (increased aberrations but no increase in sister chromatid exchange) was reported in another (Nordenson et al. 1979). Moore et al. (1997a) reported an exposure-dependent increase in the prevalence of micronucleated cells in a Chilean male population chronically exposed to high and low arsenic levels in their drinking water (average concentrations, 600 and 15 µg As/L, respectively), and suggested that chromosome breakage was the major cause of micronucleus (MN)

formation. Vig et al. (1984) found no significant differences in the frequency of chromosomal aberrations or sister chromatid exchange between two populations in Nevada with differing levels of arsenic in their drinking water (mean concentrations of 5 and 109 μg/L). In animal studies, an increased incidence of chromosomal abnormalities was detected in rats given oral doses of sodium arsenate (4 mg As/kg/day) for 2–3 weeks (Datta et al. 1986), but no consistent increase in chromosomal aberrations was detected in bone marrow cells or spermatogonia from mice given sodium arsenite (about 50 mg As/kg/day) for up to 8 weeks (Poma et al. 1987). These studies suggest that ingested arsenic may cause chromosomal effects, but these data are too limited to draw a firm conclusion. Other genotoxicity studies on inorganic arsenicals are discussed in Section 2.5.

Organic Arsenicals. No studies were located regarding genotoxic effects in humans after oral exposure to organic arsenicals. An increased number of DNA strand breaks were detected in lung and other tissues of mice and rats given oral doses of DMA (Okada and Yamanaka 1994; Yamanaka et al. 1989a); this effect appeared to be related to the formation of some active oxygen species. These breaks were largely repaired within 24 hours, so the relevance with respect to health risk is uncertain. Other genotoxicity studies on organic arsenicals are discussed in Section 2.5.

2.2.2.8 Cancer

Inorganic Arsenicals. There is convincing evidence from a large number of epidemiological studies and case reports that ingestion of inorganic arsenic increases the risk of developing skin cancer (Alain et al. 1993; Bickley and Papa 1989; Cebrian et al. 1983; Haupert et al. 1996; Hsueh et al. 1995; Luchtrath 1983; Morris et al. 1974; Piontek et al. 1989; Sommers and McManus 1953; Tay and Seah 1975; Tsai et al. 1998a; Tseng 1977; Tseng et al. 1968; Zaldivar 1974; Zaldivar et al. 1981). Lesions commonly observed are multiple squamous cell carcinomas, which appear to develop from some of the hyperkeratotic warts or corns described in Section 2.2.2.2. In addition, multiple basal cell carcinomas may occur, typically arising from cells not associated with hyperkeratinization. In most cases, skin cancer develops only after prolonged exposure, but several studies have reported skin cancer in people exposed for less than 1 year (Reymann et al. 1978; Wagner et al. 1979). Although both types of skin cancer can be removed surgically, they may develop into painful lesions that may be fatal if left untreated (Shannon and Strayer 1989).

A number of studies that identify CELs in exposed humans are summarized in Table 2-3 and shown in Figure 2-3. The EPA reviewed the studies that provided dose-response data on the risk of skin cancer

(EPA 1988e) and concluded that the most useful study for the purposes of quantitative risk assessment was the ecologic epidemiology study by Tseng et al. (1968). In this study, the incidence of skin cancer was measured as a function of exposure level in over 40,000 people residing in 37 villages in Taiwan, and compared to a control group of over 7,500 people. Beyond the very large sample size, other strengths of this study include excellent case ascertainment (physical examination), inclusion of both males and females, and lifetime exposure duration. Weaknesses and uncertainties include poor nutritional status of the exposed populations, their genetic susceptibility, their exposure to inorganic arsenic from nonwater sources, and the applicability of extrapolating data from Taiwanese to the U.S. population because of different background rates of cancer, possibly genetically determined, and differences in diet other than arsenic (e.g., low protein and fat and high carbohydrate) (EPA 1988e). Because of a lack of information on the amount of individual exposure, subjects were classified into three exposure groups (i.e., high, medium, and low). Based upon pooled data and average well concentrations for each village in the Tseng et al. (1968) study, the EPA calculated a unit risk (the upper-bound excess cancer risk from lifetime exposure to water containing 1 µg As/L) of $5x10^{-5}$ (IRIS 1999). The average daily doses (expressed as mg As/kg/day) that correspond to excess cancer risks of $1x10^{-4}$ to $1x10^{-7}$ are shown in Figure 2-3.

The use of a cancer risk estimate derived from the Tseng et al. (1968) study for a U.S. population has been the source of intense debate. A number of concerns have been raised including the adequacy of the model used by EPA and the accuracy and reliability of the exposure data (Brown et al. 1997a, 1997b); a number of host and environmental factors among the Taiwanese not applicable elsewhere (Carlson-Lynch et al. 1994); a possible threshold for arsenic carcinogenicity and nonlinearities in the dose-response curve (Abernathy et al. 1996; Slayton et al. 1996); differences in health and nutrition between Taiwan and the United States that might increase cancer risk in Taiwan (Beck et al. 1995); the possibility that arsenic is an essential nutrient at lower doses (EPA 1988e; NRC 1999); and the possibility of significant exposure to arsenic from sources other than the well water (Chappell et al. 1997). These factors, many of which were recognized by EPA (1988e) at the time of the assessment, all contribute to uncertainty in the risk assessment.

Several epidemiological studies performed in the United States have not detected an increased frequency of skin cancer in small populations consuming water containing arsenic at levels of around 0.1–0.2 ppm (Goldsmith et al. 1972; Harrington et al. 1978; Morton et al. 1976; Southwick et al. 1981). These data suggest that arsenic-associated skin cancer is not a common problem in this country, but these studies lacked sufficient statistical power to detect small increases in skin cancer incidence that might have occurred at these low doses (EPA 1983g).

Wong et al. (1992) also report no evidence of skin cancer in a U.S. cohort. An ecologic study of skin cancer incidence rates was conducted from January 1980 through June 1986 in residents of four counties in Montana. The two counties considered to be exposed to arsenic were Deer Lodge, containing the former Anaconda copper smelter, and Silver Bow, containing an open pit copper mine. Residents in these counties had potential exposure to arsenic and other heavy metals. Gallatin and Park counties served as controls. Data were collected from pathology services and dermatologists in these four counties. In addition, all skin cancer cases from four dermatologists practicing in urban referral areas outside the counties were reviewed. The age-adjusted annual skin cancer rates were higher for the two control counties as compared to either the county with the former smelter, Deer Lodge, or the county with the mine, Silver Bow. The clinical features of the skin cancers in the exposed counties were not similar to those described for arsenic-related skin cancer. One of the common types of skin cancer associated with arsenic exposure (squamous cell carcinoma) was only observed in two cases in the unexposed population. The overall skin cancer incidence rates for the exposed counties were well within the range of skin cancer rates observed for other locations in the United States. The results could not be explained by differences in ascertainment, latitude, or altitude. A partial explanation could be the difference in outdoor employment. There was a higher percentage of "outside" occupations in the two nonexposed counties (9 and 15%) compared to the two exposed counties (both at 1%). The authors state that the power of the study was adequate to detect a relatively small increase in skin cancer, if one existed.

In addition to the risk of skin cancer, there is mounting evidence that ingestion of arsenic may increase the risks of internal cancers as well. Many case studies have noted the occurrence of internal tumors of the liver and other tissues in patients with arsenic-induced skin cancer (Falk et al. 1981b; Kasper et al. 1984; Koh et al. 1989; Lander et al. 1975; Regelson et al. 1968; Sommers and McManus 1953; Tay and Seah 1975; Zaldivar et al. 1981). These studies are supported by large-scale epidemiological studies, where associations and/or dose response trends have been detected for tumors of the bladder, kidney, liver, lung, and prostate (Chen and Wang 1990; Chen et al. 1985, 1986, 1988a, 1988b, 1992; Chiou et al. 1995; Cuzick et al. 1992; Ferreccio et al. 1998; Guo et al. 1997; Hopenhayn-Rich et al. 1998; Kurttio et al. 1999; Lewis et al. 1999; Rivara et al. 1997; Smith et al. 1998a; Tsuda et al. 1995a; Wu et al. 1989). The EPA has not yet calculated a unit risk value or slope factor for arsenic-induced internal tumors.

Chen et al. (1992) compared risk of various internal organ cancers induced by ingested inorganic arsenic and assessed the differences in risk between males and females. Cancer potency indices were calculated using mortality rates among residents in an endemic area of chronic arsenicism on the southwest coast of Taiwan, and with the use of the Armitage-Doll multistage model. Based on a total of 898,806 person-

years, a significant dose-response relationship was observed between arsenic level in drinking water and mortality from the cancers. Elevated mortality rates were associated with a variety of cancers including 202 liver cancers (140M, 62F), 304 lung cancers (169M, 135F), 202 bladder cancers (97M, 105F), and 64 kidney cancers (30M, 34F). The potency index of developing cancer of the liver, lung, bladder, and kidney due to an intake of 10 µg/kg/day of arsenic was estimated as $4.3x10^{-3}$, $1.2x10^{-2}$, $1.2x10^{-2}$, and $4.2x10^{-3}$, respectively, for males; and $3.6x10^{-3}$, $1.3x10^{-2}$, $1.7x10^{-2}$, and $4.8x10^{-3}$, respectively, for females in the study area. Based on the results reported by Tseng et al. (1968), the prevalence rate of skin hyperpigmentation, hyperkeratosis, or both lesions in this population were approximately 18, 7, and 6%, respectively. Thus, a substantial number of the cancer cases reported in Chen et al. (1992) may have been preceded by pre-cancerous skin lesions related to arsenic exposure.

Chiou et al. (1995) conducted a 7-year prospective cohort study in four townships in Taiwan to monitor the occurrence of internal cancers and ingested inorganic arsenic in drinking water (0–1.14 mg/L or 0–1.14 ppm). A dose-response relationship was also observed between long-term arsenic exposure from drinking artesian well water and the incidence of lung cancer, bladder cancer, and cancers of all sites combined after adjustment for age, sex, and cigarette smoking. Blackfoot patients had a significantly increased cancer incidence after adjustment for cumulative arsenic exposure.

Chow et al. (1997) compared the histopathological characteristics of As-associated (n=49) and other bladder cancers (n=64). A higher histological grading was observed for the As-exposed tumors (p=0.04), but no other difference in pathological features or prognosis was found between the two groups.

Smith et al. (1992) used the large Taiwan population and high arsenic levels in well water (170–800 µg/L) to establish dose-response relationships between cancer risks and the concentration of inorganic arsenic naturally present in water supplies. It was estimated that at the current EPA standard of 50 µg/L, the lifetime risk of dying from cancer of the liver, lung, kidney, or bladder from drinking 1 L/day of water could be as high as 13 per 1,000 persons. It has been estimated that more than 350,000 people in the United States may be supplied with water containing more than 50 µg/L arsenic, and more than 2.5 million people may be supplied with water with levels above 25 µg/L. For average arsenic levels and water consumption patterns in the United States, the risk estimate was around 1/1,000. Ingestion of arsenic, both from water supplies and medicinal preparations, is known to cause skin cancer. The authors state that the evidence assessed here indicates that arsenic can also cause liver, lung, kidney, and bladder cancer and that the population cancer risks due to arsenic in U.S. water supplies may be comparable to those from environmental tobacco smoke and radon in homes. Although further research

is needed to validate these findings, the authors believed that measures to reduce arsenic levels in water supplies should be considered.

In a similar vein, Moore et al. (1997a) report the results from a cross-sectional biomarker study in a Chilean male population chronically exposed to high and low arsenic levels in their drinking water (average concentrations, 600 and 15 µg As/L, respectively). A fluorescent version of the exfoliated bladder cell MN assay was used employing fluorescence *in situ* hybridization with a centromeric probe to identify the presence (MN+) or absence (MN-) of whole chromosomes within micronuclei to investigate the mechanism of arsenic-induced genotoxicity *in vivo*. The results showed an exposure-dependent increase in prevalence of micronucleated cells and suggested that chromosome breakage was the major cause of MN formation. Prevalence of total MN, MN+, and MN- returned to baseline levels for urinary arsenic in the highest group (729–1,894 µg/L), perhaps due to cytostasis or cytotoxicity. Inorganic arsenic is an established cause of lung and skin cancer. These results add additional weight to the hypothesis that ingesting arsenic-contaminated water enhances bladder cancer risk and suggest that arsenic induces genetic damage to bladder cells at drinking water levels close to the current U.S. Maximum Contaminant Level (MCL) of 50 µg/L for arsenic.

Yu et al. (1992) report the effects of arsenic on the mitogenic responses of mononuclear cells (MNC) derived from patients with arsenical skin cancers from an arsenic endemic area on the southwest coast of Taiwan. The subjects enrolled in this study included patients with Bowen's disease, arsenical skin cancers (basal cell carcinoma and squamous cell carcinoma), non-arsenical skin cancers (basal cell carcinoma and squamous cell carcinoma), nasopharyngeal cancer, and healthy controls from endemic and non-endemic areas. Phytohemagglutinin (PHA) stimulated [^{3}H]thymidine incorporation in MNC in all groups except the arsenical skin cancer group. However, when a low concentration of As_2O_3 ($2.5x10^{-7}$ M) was added to PHA-stimulated MNC, a tremendous amplification of the uptake of [^{3}H]thymidine was noticed in patients with arsenical skin cancer. In this study, this phenomenon did not occur in cancers not related to arsenic. This result suggests that arsenical carcinomas are hyperreactive to arsenic. Arsenic seems to play a role as a co-stimulant of PHA similar to interleukin-1.

Hsueh et al. (1995) conducted a cross-sectional study to evaluate the prevalence of arsenic-induced skin cancer among residents in Taiwanese villages exposed to inorganic arsenic in drinking water (0–0.93 ppm). A dose-response increase in skin cancer was associated with arsenic. There was also an increase in skin cancers associated with carriers of hepatitis B surface antigen with liver dysfunction, and

undernourishment. This study supports concerns about the differences between the Taiwanese and U.S. populations.

Hopenhayn-Rich et al. (1996a) investigated bladder cancer mortality for the years 1986–1991 in the 26 counties of Cordoba, Argentina. Rates for all of Argentina were used as the standard for comparison. Several areas of Argentina have had high exposures to arsenic from naturally contaminated drinking water, particularly the eastern region of the province of Cordoba. Bladder cancer SMRs were consistently higher in counties with documented arsenic exposure. The clear trends found in this Argentina population with different genetic composition and a high-protein diet support the findings in Taiwan of dose-response relation between ingestion of inorganic arsenic from drinking water and bladder cancer.

Cuzick et al. (1992) evaluated a cohort treated with Fowler's solution (potassium arsenite) in Lancashire, England, during the period 1945–1969. These results add 11 years to the initial study results that followed the cohort until January 1, 1980. The cohort of 478 patients showed a significant excess of bladder cancer mortality (observed/expected ratio=5/1.6; p=0.05). No excess was found for other causes of death. Of a subcohort of 142 patients examined for signs of arsenicism around 1970, all 11 subsequent cancer deaths occurred in those with signs of arsenicism (p=0.0009).

Wulff et al. (1996) conducted a retrospective study of a cohort of children born between 1961 and 1990 in the municipality of Skelleftea, Sweden, where a smelter released arsenic and other pollutants including lead, copper, cadmium, sulfur dioxide, and possibly other emissions such as nickel and selenium. Childhood cancer incidences among children born in the vicinity of the smelter (i.e., within 20 km) and distant from the smelter (>20 km) were compared with expected incidences based on Swedish national statistics. There appeared to be an increased risk of childhood cancer (all types combined) among children born in the vicinity of the smelter (SIR=195, 95% CI=88–300, based on 13 cases observed and 6.7 expected), but the increase was not statistically significant, and in any event, the role of arsenic in any finding from this study is confounded by the presence of other metals. The number of cases (n=42) was very close to the expected number (n=41.8) among children born distant from the smelter.

Studies in U.S. populations exposed to arsenic in drinking water (Morton et al. 1976; Southwick et al. 1981; Valentine et al. 1992) have not yielded the cancer incidences and health effects noted in Taiwan, Mexico, and Chile. Whether this difference is due to a smaller population of subjects compared to Taiwan, to overall lower doses in exposed U.S. populations, or to differences in nutritional or

socioeconomic conditions has not been resolved. It should be noted that exposed populations in Mexico and Chile are also smaller than those in Taiwan.

Most studies of animals exposed to arsenate or arsenite by the oral route have not detected any clear evidence for an increased incidence of skin cancer or other cancers (Byron et al. 1967; Kroes et al. 1974; Schroeder et al. 1968). Arsenic has sometimes been called a “paradoxical” human carcinogen because of this lack of animal data (Jager and Ostrosky-Wegman 1997). The basis for the lack of tumorigenicity in animals is not known, but could be related to species-specific differences in arsenic distribution, and induction of cell proliferation (Byrd et al. 1996) (see Section 2.3). Chan and Huff (1997) argue that a carefully controlled long-term carcinogenesis bioassay (i.e., using the National Toxicology Program protocol) has not been conducted for either arsenic trioxide by inhalation exposure or for sodium arsenite by drinking water. Thus, statements as to the paradoxical nature of arsenic as a human carcinogen are premature.

One mouse study using transgenic mice (which carry the v-Ha-ras oncogene) administered 48 mg As/kg/day as sodium arsenite in drinking water for 4 weeks followed by dermal application of 12-O-tetradecanoylphorbol-13-acetage (TPA) to shaved back skin twice a day for 2 weeks showed an increase in incidence of skin papillomas when compared to transgenic mice receiving only TPA treatment or only arsenic or to wild-type mice receiving both TPA and arsenic (Germolec et al. 1998). Increases in mRNA transcripts for the growth factors transforming growth factor-α (TGF-α) and granulocyte/ macrophage-colony stimulating factor (GM-CSF) were detected in the epidermis of the arsenic-treated mice.

A few studies in mice have noted that arsenic ingestion may actually decrease the incidence of some tumor types. For example, arsenic exposure caused decreased incidence of urethane-induced pulmonary tumors (Blakley 1987), spontaneous mammary tumors (Schrauzer and Ishmael 1974; Schrauzer et al. 1976), and tumors resulting from injection of mouse sarcoma cells (Kerkvliet et al. 1980). However, arsenic also increased the growth rate of the tumors which did occur, resulting in a net decrease in survival time in tumor-bearing animals (Kerkvliet et al. 1980; Schrauzer and Ishmael 1974). These observations suggest that arsenic may affect different types of neoplastic cells differently, perhaps acting mainly as a tumor promoter (Schrauzer and Ishmael 1974; Shirachi et al. 1983). However, these data do not suggest that arsenic should be viewed as having any net therapeutic "anti-cancer" effect.

Organic Arsenicals. No studies were located regarding cancer in humans after oral exposure to organic arsenicals. In an early 2-year study of roxarsone toxicity in animals, no increase in tumor frequency was detected in dogs given 1.5 mg As/kg/day, rats given 2.9 mg As/kg/day, or mice given 3.8 mg As/kg/day (Prier et al. 1963). More recently, lifetime studies of roxarsone at doses up to 1.4 mg As/kg/day yielded no evidence of carcinogenicity in male or female mice or female rats, but a slight increase in pancreatic tumors was noted in male rats (NTP 1989b). This was considered to constitute equivocal evidence of carcinogenicity. The incidence of basophilic foci (believed to be a precancerous lesion) in liver of rats initiated with diethylnitrosamine was increased by subsequent exposure to DMA, suggesting that this compound could act as a cancer promoter (Johansen et al. 1984).

Yamamoto et al. (1995) also evaluated the carcinogenic effects of DMA in rats in a multiorgan carcinogenesis bioassay. Male F344/DuCrj rats were treated sequentially with diethylnitrosamine (DEN) and N-methyl-N-nitrosamine (MNU), then 1,2-dimethylhydrazine (DMH). The animals were then sequentially administered N-butyl-N-(4-hyroxybutyl)nitrosamine (BBN) in drinking water in weeks 1 and 2 and N-bis(2-hyroxypropyl)nitrosamine (DHPN) in drinking water during weeks 3 and 4. This is referred to as the DMBDD treatment. After a 2-week interval, rats were given 50, 100, 200, or 400 ppm DMA in drinking water. DMA significantly enhanced the tumor induction in the urinary bladder, kidney, liver, and thyroid gland in DMBDD-treated groups. Induction of preneoplastic lesions (glutathione S-transferase placental form-positive foci in the liver and atypical tubules in the kidney) was also significantly increased in DMA-treated groups. DMA thus acted as a promoter of urinary bladder, kidney, liver, and thyroid gland carcinogenesis in rats.

A study by Li et al. (1998b) further evaluating the promotional effects of DMA on bladder cancer exposed NBR rats (which do not synthesize $\alpha_{2\mu}$-globulin) to BBN in drinking water for 4 weeks, followed by 100 ppm DMA in drinking water for 32 weeks. A statistically significant increase in simple hyperplasia and papillary or nodular hyperplasia of the bladder and a non-statistically significant increase in papilloma carcinoma was observed.

Wanibuchi et al. (1996) evaluated the promoting and carcinogenic effects of DMA in a male F344/DuCrj rat urinary bladder carcinogenicity model. Rats were administered BBN in drinking water during weeks 1–4, then received 0, 2, 10, 25, 50, or 100 ppm DMA in drinking water for an additional 32 weeks. For 100 ppm of DMA with no BBN pretreatment, there were no urinary bladder papillomas or carcinomas observed. DMA with BBN pretreatment resulted in a dose-dependent increase in both the incidence and multiplicity of tumors, clearly demonstrating the promoting effects of DMA in this model.

Yamamoto et al. (1997) evaluated the promoting and carcinogenic effects of DMA in a medium-term, two-step, rat hepatocarcinogenesis model. Male F344/DuCrj rats were treated with a single intraperitoneal dose of DEN, then 2 weeks later with either 0, 25, 50, or 100 ppm DMA in drinking water. Animals in all groups were subjected to a two-thirds partial hepatectomy at week 3 to maximize any interaction between proliferations and the effects of DMA. The number and areas of glutathione S-transferase placental form (GST-P) positive foci per unit of liver sections increased in the DMA-treated groups with significant enhancement of hepatocarcinogenesis observed with 50 ppm DMA and above.

Hayashi et al. (1998) evaluated the effects of DMA on lung tumorigenesis. Small (not statistically significant) increases in percent tumor-bearing mice and number of tumors per mouse in mice receiving 50 or 200 ppm DMA in drinking water for 50 weeks were observed. Mice receiving 400 ppm DMA showed significant increases in number of tumors per mouse.

The above studies with DMA are limited, but they do provide some evidence that organic arsenicals can promote carcinogenicity and may act as weak carcinogens.

These data are too limited to draw firm conclusions, but it appears that organic arsenicals might possess weak carcinogenic potential.

2.2.3 Dermal Exposure

Adverse effects from dermal exposure to inorganic or organic arsenicals have not been extensively investigated. Table 2-5 summarizes studies in animals and humans which provide quantitative data on dermal exposure-effect relationships for inorganic arsenicals. No quantitative data on dermal exposure to organic arsenicals were located. Available quantitative and qualitative data are discussed in greater detail below.

2.2.3.1 Death

Inorganic Arsenicals. No studies were located regarding death in humans after dermal exposure to inorganic arsenicals. In rats, no deaths resulted from dermal exposure to arsenate or arsenite at doses up to 1,000 mg As/kg (Gaines 1960). These data indicate that dermal exposure to inorganic arsenic compounds is very unlikely to result in death.

Table 2-5. Levels of Significant Exposure to Inorganic Arsenic - Dermal

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL		Reference Chemical Form
					Less Serious	Serious	
ACUTE EXPOSURE							
Immunological/Lymphoreticular							
	Gn pig (Hartley)	once		580 mg/L			Wahlberg and Boman 1986 As(+3)
	Gn pig (Hartley)	once		4000 mg/L			Wahlberg and Boman 1986 As(+5)
INTERMEDIATE EXPOSURE							
Systemic							
	Mouse (Rockland)	30 wk 11x/wk	Dermal		6 mg/kg/day F	(gross hyperplasia, ulceration)	Boutwell 1963 As(+3)

F = female; Gn pig = guinea pig; wk = week(s); x = time(s).

Organic Arsenicals. No studies were located regarding death in humans or animals after dermal exposure to organic arsenicals.

2.2.3.2 Systemic Effects

No studies were located that have associated respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, or renal effects in humans or animals to dermal exposure to inorganic or organic arsenicals.

Dermal Effects

Inorganic Arsenicals. Several studies of humans exposed to arsenic dusts in the workplace have reported that inorganic arsenic (usually arsenic trioxide) can cause contact dermatitis (Holmqvist 1951; Pinto and McGill 1953). Typical responses included erythema and swelling, with papules and vesicles in more severe cases (Holmqvist 1951). The dermal contact rates that cause these effects in humans have not been quantified, but a similar direct irritation of the skin has been noted in mice exposed to 4 mg As/kg/day as potassium arsenite for 30 weeks (Boutwell 1963). In contrast, no significant dermal irritation was noted in guinea pigs exposed to aqueous solutions containing 4,000 mg As/L as arsenate or 580 mg As/L as arsenite (Wahlberg and Boman 1986). These studies indicate that direct contact may be of concern at high exposure levels, but do not suggest that lower levels are likely to cause significant irritation.

Studies on possible dermal sensitization by inorganic arsenicals are discussed in Section 2.2.3.3 below.

Organic Arsenicals. Application of MMA to the skin of rabbits was reported to result in mild dermal irritation (Jaghabir et al. 1988), but too few details on dose, duration, or degree of irritation were provided to draw firm conclusions regarding the dermal irritancy of organic arsenicals.

Ocular Effects

Inorganic Arsenicals. No studies were located regarding ocular effects in humans or animals after dermal exposure to inorganic arsenicals.

Organic Arsenicals. Application of MMA to the skin of rabbits was reported to result in mild dermal irritation (Jaghabir et al. 1988), but too few details on dose, duration, or degree of irritation were provided to draw firm conclusions regarding the ocular irritancy of organic arsenicals.

2.2.3.3 Immunological and Lymphoreticular Effects

Inorganic Arsenicals. Examination of workers exposed to arsenic trioxide dusts in a copper smelter led Holmqvist (1951) to suspect that repeated dermal contact could lead to dermal sensitization. In support of this, Holmqvist (1951) found a positive patch test in 80% of the exposed workers compared to 30% in a control population. These data do suggest that workers may be sensitized to arsenic, but the high response rate in controls seems unusual. A much lower response rate (0.5%) was noted in a more recent patch test study of dermal sensitization (Wahlberg and Boman 1986), and the few positive responses seemed to be due to a cross-reactivity with nickel. Mohamed (1998) evaluated 11 male workers at a tin smelting factory where arsenic trioxide levels ranged from 5.2 to 14.4 mg/m^3. The workers experienced symptoms of generalized itch, dry and hyperpigmented skin, folliculitis, and superficial ulcerations. The authors concluded that arsenic-containing dust collected on the sweat on the workers' skin, causing contact dermatitis. Studies in guinea pigs did not yield evidence of a sensitization reaction to inorganic arsenic (Wahlberg and Boman 1986).

Organic Arsenicals. Support for sensitization to DMA is provided in a case control study of a 26-year-old woman who was occupationally exposed to DMA and experienced eczema on her face (Bourrain et al. 1998). Patch testing confirmed an allergic reaction to DMA, and avoidance of DMA resulted in disappearance of the symptoms. No studies were located regarding immunological or lymphoreticular effects in animals after dermal exposure to organic arsenicals.

No studies were located that have associated any of the following effects in humans or animals to dermal exposure to inorganic or organic arsenicals:

2.2.3.4 Neurological Effects

2.2.3.5 Reproductive Effects

2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.3.8 Cancer

Inorganic Arsenicals. No studies were found that have associated cancer in humans with dermal exposure to arsenic. Application of arsenic acid to the skin of mice pretreated with dimethylbenzanthracene did not result in any skin tumors (Kurokawa et al. 1989), suggesting that arsenic does not act as a promoter in this test system.

Organic Arsenicals. No studies were located regarding cancer in humans or animals after dermal exposure to organic arsenicals.

2.3 TOXICOKINETICS

There is an extensive database on the toxicokinetics of inorganic arsenic. Most studies have been performed in animals, but there are a number of studies in humans as well. These studies reveal the following main points:

- Both arsenate and arsenite are well absorbed by both the oral and inhalation routes. Absorption by the dermal route has not been well characterized, but is low compared to the other routes. Inorganic arsenic in soil is absorbed to a lesser extent than solutions of arsenic salts.

- The rate of absorption of arsenic in highly insoluble forms (e.g., arsenic sulfide, lead arsenate) is much lower than that of more soluble forms via both oral and inhalation routes.

- Once absorbed, arsenites are partially oxidized to arsenates and arsenates are partially reduced to arsenites, yielding a mixture of As(+3) and As(+5) in the blood.

- Distribution of arsenic in the rat is quite different from other animal species, suggesting that the rat is probably not an appropriate toxicokinetic model for distribution, metabolism, or excretion of arsenic by humans.

- The As(+3) form undergoes enzymic methylation primarily in the liver to form MMA and DMA. The rate and relative proportion of methylation production varies among species. The rate of methylation may also vary among tissues.

- Most arsenic is promptly excreted in the urine as a mixture of As(+3), As(+5), MMA, and DMA. Smaller amounts are excreted in feces. Some arsenic may remain bound to tissues, depending inversely on the rate and extent of methylation.

Less information is available for the organic arsenicals. It appears that both MMA and DMA are well absorbed, but are rapidly excreted in the urine and feces. MMA may be methylated to DMA, but neither MMA nor DMA are demethylated to yield inorganic arsenic.

A review of the evidence which supports these conclusions is presented below.

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

Since arsenic exists in air as particulate matter, absorption across the lung involves two processes: deposition of the particles onto the lung surface, and absorption of arsenic from the deposited material. In lung cancer patients exposed to arsenic in cigarette smoke, deposition was estimated to be about 40% and absorption was 75–85% (Holland et al. 1959). Thus, overall absorption (expressed as a percentage of inhaled arsenic) was about 30–34%. In workers exposed to arsenic trioxide dusts in smelters, the amount of arsenic excreted in the urine (the main route of excretion; see Section 2.3.4) was about 40–60% of the estimated inhaled dose (Pinto et al. 1976; Vahter et al. 1986). Absorption of arsenic trioxide dusts and fumes (assessed by measurement of urinary metabolites) correlated with time weighted average arsenic air concentrations from personal breathing zone air samplers (Offergelt et al. 1992). Correlations were best immediately after a shift and just before the start of the next shift. Although the percent deposition was not measured in these cases, it seems likely that nearly all of the deposited arsenic was absorbed. This conclusion is supported by intratracheal instillation studies in rats and hamsters, where clearance of oxy compounds of arsenic (sodium arsenite, sodium arsenate, arsenic trioxide) from the lung was rapid and nearly complete (60–90% within 1 day) (Marafante and Vahter 1987; Rhoads and Sanders 1985). In contrast, arsenic sulfide and lead arsenate were cleared more slowly (Marafante and Vahter 1987),

indicating that the rate of absorption may be lower if the inhaled arsenic is in a highly insoluble form. There are no data to suggest that absorption of inhaled arsenic in children differs from that in adults.

No studies were located regarding absorption of organic arsenicals in humans or animals after inhalation exposure. However, DMA instilled in the lungs of rats was absorbed very rapidly (half-time of 2.2 minutes) and nearly completely (at least 92%) (Stevens et al. 1977b). This indicates that organic arsenicals are likely to be well absorbed by the inhalation route.

2.3.1.2 Oral Exposure

Several studies in humans indicate that arsenates and arsenites are well absorbed across the gastrointestinal tract. The most direct evidence is from measurement of fecal excretion in humans given oral doses of arsenite, where less than 5% was recovered in the feces (Bettley and O'Shea 1975). This indicates absorption was at least 95%. This is supported by studies in which urinary excretion in humans was found to account for 55–80% of daily oral intakes of arsenate or arsenite (Buchet et al. 1981b; Crecelius 1977; Mappes 1977; Tam et al. 1979b). In contrast, ingestion of arsenic triselenide (As_2Se_3) did not lead to a measurable increase in urinary excretion (Mappes 1977), indicating that gastrointestinal absorption may be much lower if highly insoluble forms of arsenic are ingested. There are no data to suggest that absorption of arsenic from the gut in children differs from that in adults.

These observations in humans are supported by a number of studies in animals. Fecal excretion of arsenates and arsenites ranged from 2 to 10% in monkeys and mice, with 70% or more appearing in urine (Charbonneau et al. 1978a; Vahter 1981; Vahter and Norin 1980). Oral absorption of [^{73}As] labeled sodium arsenate in mice was unaffected by dose (0.0005–5 mg/kg) as reflected in percentage of dose excreted in feces over 48 hours (Hughes et al. 1994). Absorption ranged from 82 to 89% at all doses. Gonzalez et al. (1995) found that the percentage of arsenate that was absorbed in rats decreased as the dose increased from 6 to 480 µg, suggesting saturable, zero-order absorption of arsenate in this species. Hamsters appear to absorb somewhat less than humans, monkeys, and mice, since fecal excretion usually ranges from 10 to 40% (Marafante and Vahter 1987; Marafante et al. 1987a; Yamauchi and Yamamura 1985). Rabbits also appear to absorb less arsenate than humans, monkeys, or mice after oral exposure (Freeman et al. 1993). After a gavage dose of 1.95 mg/kg sodium arsenate, 45% of the arsenate was recovered in feces in males and 52% in females. As in humans, when highly insoluble arsenic compounds are administered (arsenic trisulfide, lead arsenate), gastrointestinal absorption is reduced 20–30% (Marafante and Vahter 1987).

Bioavailability of arsenic was measured in rabbits ingesting doses of smelting soils which contained arsenic primarily in the form of sulfides (Freeman et al. 1993). Bioavailability was assessed by comparing the amounts of arsenic that was excreted after ingestion of the soil to that excreted after an intravenous dose of sodium arsenate. The bioavailability of the arsenic in the ingested soil was 24±3.2% and that of sodium arsenate in the gavage dose was 50±5.7%. Approximately 80% of the arsenic from ingested soil was eliminated in the feces compared with 50% of the soluble oral dose and 10% of the injected dose. In another study, rabbits dosed with sodium arsenite (0.8 mg As/kg) had 5 times greater blood arsenic concentrations than rabbits dosed with arsenic-containing soil (2.8 mg As/kg), suggesting a lower bioavailability of the arsenic in soil (Davis et al. 1992).

Studies of the bioavailability of arsenic suggest that absorption of arsenic in ingested dust or soil is likely to be considerably less than absorption of arsenic from ingested salts (Davis et al. 1992, 1996; EPA 1997g; Freeman et al. 1993, 1995; Pascoe et al. 1994; Rodriguez et al. 1999). Oral absorption of arsenic in a group of three female Cynomolgus monkeys from a soluble salt, soil, and household dust was compared with absorption of an intravenous dose of sodium arsenate (Freeman et al. 1995). Mean absolute percentage bioavailability based on urine arsenic excretion was reported at 67.6±2.6% (gavage), 19.2±1.5% (oral dust), and 13.8±3.3% (oral soil). Mean absolute percentage bioavailability based on blood arsenic levels was reported at 91.3±12.4% (gavage), 9.8±4.3% (oral dust), and 10.9±5.2% (oral soil). The arsenic in the dust and soil was approximately 3.5–5-fold (based on urine) and 8–9-fold (based on blood) less bioavailable than arsenic in solution. A study in beagle dogs fed with soil containing As_2O_5 or treated with intravenous soluble arsenic found that compared to injection the bioavailability of arsenic from ingested soil was 8.3±2.0% (Groen et al. 1993). The bioavailability of arsenic in soil has been studied in juvenile swine that received daily oral doses of soil or sodium arsenate (in food or by gavage) for 15 days (EPA 1997g). The soils were obtained from various mining and smelting sites and contained, in addition to arsenic at concentrations of 100–300 µg/g, lead at concentrations of 3,000–14,000 µg/g. The arsenic doses ranged from 1 to 65.4 µg/kg/day. The fraction of the arsenic dose excreted in urine was measured on days 7 and 14 and the relative bioavailability of the soil-borne arsenic was estimated as the ratio of urinary excretion fractions, soil arsenic:sodium arsenate. The mean relative bioavailability of soil-borne arsenic ranged from 0 to 98% in soils from seven different sites (mean±SD, 45%±32). Estimates for relative bioavailability of arsenic in samples of smelter slag and mine tailings ranged from 7 to 51% (mean±SD, 35%±27). Rodriguez et al. (1999) used a similar approach to estimate the relative bioavailability of arsenic in mine and smelter wastes (soils and solid materials) in juvenile swine. Samples included iron slag deposits and calcine deposits and had arsenic concentrations that ranged from 330 to 17,500 µg/g. Relative bioavailability (waste:sodium arsenate) ranged from 3 to 43%

for 13 samples (mean, 21%) and was higher in iron slag wastes (mean, 25%) than in calcine wastes (mean, 13%).

Bioavailability of arsenic from soil is reduced by low solubility and inaccessibility due to the presence of secondary reaction products or insoluble matrix components (Davis et al. 1992). This is supported by studies conducted with *in vitro* simulations of the gastric and/or intestinal fluids (Hamel et al. 1998; Rodriguez et al. 1999; Ruby et al. 1996, 1999; Williams et al. 1998). When soils containing arsenic are incubated in simulated gastrointestinal fluids, only a fraction of the arsenic becomes soluble. Estimates of the soluble, or bioaccessible, arsenic fraction have ranged from 3 to 50% for various soils and mining and smelter waste materials (Rodriguez et al. 1999; Ruby et al. 1996); these estimates are similar to *in vivo* estimates of the relative bioavailability of arsenic in these same materials (Ruby et al. 1999).

Based on urinary excretion studies in volunteers, it appears that both MMA and DMA are well absorbed (at least 75–85%) across the gastrointestinal tract (Buchet et al. 1981a; Marafante et al. 1987b). This is supported by studies in animals, where at least 75% absorption has been observed for DMA (Marafante et al. 1987b; Stevens et al. 1977b; Yamauchi and Yamamura 1984) and MMA (Yamauchi et al. 1988).

2.3.1.3 Dermal Exposure

No quantitative studies were located on absorption of inorganic arsenicals in humans after dermal exposure. Percutaneous absorption of [^{73}As] as arsenic acid (H_3AsO_4) alone and mixed with soil has been measured in skin from cadavers (Wester et al. 1993). Labeled arsenic was applied to skin in diffusion cells and transit through the skin into receptor fluid measured. After 24 hours, 0.93% of the dose passed through the skin and 0.98% remained in the skin after washing. Absorption was lower with [^{73}As] mixed with soil: 0.43% passed through the skin over 24 hours and 0.33% remained in the skin after washing.

Dermal absorption of arsenic has been measured in Rhesus monkeys (Wester et al. 1993). After 24 hours, 6.4% of [^{73}As] as arsenic acid was absorbed systemically, as was 4.5% of [^{73}As] mixed with soil. Uptake of arsenic into blood or tissues was undetectable for up to 24 hours in rats whose tails were immersed in solutions of sodium arsenate for 1 hour. However, arsenic began to increase in blood, liver, and spleen over the next 5 days (Dutkiewicz 1977). The rate of uptake was estimated to be 1–33 µg/cm^2/hour. These findings suggest that dermal exposure leads initially to arsenic binding to skin, and that the bound arsenic may slowly be taken up into the blood, even after exposure ends.

No studies were located on absorption of organic arsenicals in humans or animals after dermal exposure.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No studies were located on the distribution of arsenic in humans or animals after inhalation exposure, but intratracheal administration of arsenic trioxide to rats resulted in distribution of arsenic to the liver, kidney, skeleton, gastrointestinal tract, and other tissues (Rhoads and Sanders 1985). This is consistent with data from oral and parenteral studies (below) which indicate that absorbed arsenic is distributed throughout the body.

No studies were located regarding the distribution of organic arsenicals in humans or animals after inhalation exposure. However, DMA administered to rats by the intratracheal route was distributed throughout the body (Stevens et al. 1977b), suggesting that inhalation of organic arsenicals would also lead to widespread distribution.

2.3.2.2 Oral Exposure

Analysis of tissues taken at autopsy from people who were exposed to background levels of arsenic in food and water revealed that arsenic is present in all tissues of the body (Liebscher and Smith 1968). Most tissues had about the same concentration level (0.05–0.15 ppm), while levels in hair (0.65 ppm) and nails (0.36 ppm) were somewhat higher. This indicates that there is little tendency for arsenic to accumulate preferentially in any internal organs. However, exposure levels may not have been high enough to cause elevated levels in tissues. Arsenic exposure may have been low enough that the methylation process in the body resulted in limited accumulation in internal organs. Tissue analysis of organs taken from an individual following death from ingestion of 8 g of arsenic trioxide (about 3 g of arsenic) showed a much higher concentration of arsenic in liver (147 μg/g) than in kidney (27 μg/g) or muscle, heart, spleen, pancreas, lungs, or cerebellum (11–12 μg/g) (Benramdane et al. 1999). Small amounts were also found in other parts of the brain (8 μg/g), skin (3 μg/g), and hemolyzed blood (0.4 μg/g). Many studies have been performed where arsenic levels in hair and nails have been measured and correlations with exposure analyzed. Some of these studies are discussed in Section 2.7, Biomarkers of Exposure.

Inorganic arsenic passes easily through the placenta. High levels of arsenic were found in the liver, kidney, and brain during autopsy of an infant prematurely born to a young mother who had ingested inorganic arsenic at 30-week pregnancy (Lugo et al. 1969). Arsenic was detected in human breast milk at concentrations of 0.00013–0.00082 ppm in a World Health Organization study (Somogyi and Beck 1993). Arsenic concentrations were 0.0001–0.0044 ppm in human milk sampled from 88 mothers on the Faroe Islands whose diets were predominantly seafood (Grandjean et al. 1995). Exposures to arsenic from the seafood diet in this population was most likely to organic "fish arsenic." In a population of Andean women exposed to high concentrations (about 200 ppb) of inorganic arsenic in drinking water, concentrations of arsenic in breast milk ranged from about 0.0008 to 0.008 ppm (Concha et al. 1998b).

Studies in mice and hamsters given oral doses of arsenate or arsenite have found elevated levels of arsenic in all tissues examined (Vahter and Norin 1980; Yamauchi and Yamamura 1985), including the placenta and fetus of pregnant females (Hood et al. 1987, 1988). Inorganic arsenic crosses the placental barrier and selectively accumulates in the neuroepithelium of the developing animal embryo (Hanlon and Ferm 1977; Lindgren et al. 1984). In mice, radiolabel from orally administered 74-As was widely distributed to all tissues, with the highest levels in kidney and liver. No obvious differences between As(+3) and As(+5) were found, although residual levels after 24 hours tended to be higher for As(+3) than As(+5) (Vahter and Norin 1980). In hamsters, increases in tissue levels were noted after oral treatment with As(+3) for most tissues (hair, kidney, liver, lung, skin, muscle), with the largest increases in liver and lung (Yamauchi and Yamamura 1985). Liver and kidney arsenic concentations increased with dose in dogs fed arsenite in the diet for 6 months (Neiger and Osweiler 1992).

No studies were located on the distribution of organic arsenicals in people following oral exposure, but MMA and DMA formed *in vivo* by methylation of inorganic arsenic in hamsters appears to be distributed to all tissues (Takahashi et al. 1988; Yamauchi and Yamamura 1985). This is supported by studies in animals, in which MMA and DMA were found in all tissues after acute oral doses (Stevens et al. 1977b; Yamauchi and Yamamura 1984; Yamauchi et al. 1988).

2.3.2.3 Dermal Exposure

No studies were located regarding distribution of inorganic or organic arsenicals in humans or animals after dermal exposure.

2.3.2.4 Other Routes of Exposure

Studies in mice, rabbits, and monkeys injected intravenously with solutions of arsenite or arsenate confirm that arsenic is widely distributed throughout the body (Lindgren et al. 1982; Marafante and Vahter 1986; Vahter and Marafante 1983; Vahter et al. 1982). Shortly after exposure, the concentration of arsenic tends to be somewhat higher in liver, kidney, lung, and gastrointestinal epithelium (Lindgren et al. 1982; Vahter and Marafante 1983; Vahter et al. 1982), but levels tend to equilibrate over time. Arsenate shows a tendency to deposit in skeletal tissue that is not shared by arsenite (Lindgren et al. 1982, 1984), presumably because arsenate is an analog of phosphate.

The distribution of arsenic in the rat is quite different from other animal species. Following intramuscular injection of carrier-free radio-arsenate in rats, most of the injected arsenic became bound to hemoglobin in red blood cells, and very little reached other tissues (Lanz et al. 1950). However, similar experiments in dogs, mice, guinea pigs, rabbits, and chicks found very little uptake of arsenic into the blood in these species (cats gave intermediate results).

2.3.3 Metabolism

The metabolism of inorganic arsenic has been extensively studied in humans and animals. Two processes are involved: (1) reduction/oxidation reactions that interconvert arsenate and arsenite, and (2) methylation reactions, which convert arsenite to MMA and DMA. These processes appear to be similar whether exposure is by the inhalation, oral, or parenteral route. The human body has the ability to change inorganic arsenic to less toxic organic forms (i.e., by methylation) that are more readily excreted in urine. In addition, inorganic arsenic is also directly excreted in the urine. It is estimated that by means of these two processes, more than 75% of the absorbed arsenic dose is excreted in the urine (Marcus and Rispin 1988). Long-term accommodation to arsenic exposure is also possible in which methylation and excretion become more efficient with several months of exposure. This mechanism is thought to have an upper-dose limit which, when overwhelmed, results in a higher incidence of arsenic toxicity. This is supported by a case report of an individual who died 3 days after ingesting 8 g of arsenic trioxide (about 3 g of arsenic) (Benramdane et al. 1999). Only 20% of the total arsenic in all tissues analyzed was methylated (14% MMA, 6% DMA), while 78% remained as arsenite and 2% as arsenate.

The basic type of evidence that supports these conclusions is derived from analysis of urinary excretion products. Exposure of humans to either arsenates or arsenites results in increased levels of inorganic

As(+3), inorganic As(+5), MMA, and DMA in urine (Buchet et al. 1981a, 1981b; Concha et al. 1998a, 1998b; Crecelius 1977; Kurttio et al. 1998; Lovell and Farmer 1985; Smith et al. 1977; Tam et al. 1979b; Vahter 1986). Similar results are obtained from studies in mice (Vahter 1981; Vahter and Envall 1983), hamsters (Hirata et al. 1988; Marafante and Vahter 1987; Takahashi et al. 1988), and rabbits (Maiorino and Aposhian 1985; Marafante et al. 1985; Vahter and Marafante 1983).

The relative proportions of As(+3), As(+5), MMA, and DMA in urine can vary depending upon the chemical administered, time after exposure, route of exposure, dose level, and exposed species. In general, however, DMA is the principal metabolite, with lower levels of inorganic arsenic [As(+3) and As(+5)] and MMA. In humans, the relative proportions are usually about 40–60% DMA, 20–25% inorganic arsenic, and 15–25% MMA (Buchet et al. 1981a; Smith et al. 1977; Tam et al. 1979b; Vahter 1986). One study of groups of women and children in two villages in Argentina showed that children ingesting large amounts of arsenic in their drinking water (200 µg/L) excreted about 49% inorganic arsenic and 47% DMA (Concha et al. 1998b). This compared to 32% inorganic arsenic and 66% DMA for the women in the study. This may indicate that metabolism of arsenic in children is less efficient than in adults. The rabbit has a ratio of metabolites similar to human adults (Maiorino and Aposhian 1985), suggesting that this may be the best animal model for toxicokinetics in humans. In contrast, the guinea pig and the marmoset and tamarin monkeys do not methylate inorganic arsenic (Healy et al. 1998; Vahter and Marafante 1985; Vahter et al. 1982; Zakharyan et al. 1996), and so may be poor models for humans.

Reduction of arsenate to arsenite can be mediated by glutathione (Menzel et al. 1994). Scott et al. (1993) showed that glutathione forms complexes with both arsenate and arsenite *in vitro*, and that glutathione is oxidized (and arsenate reduced) in the glutathione-arsenate reaction. Studies *in vitro* indicate that the substrate for methylation is As(+3), and that As(+5) is not methylated unless it is first reduced to As(+3) (Buchet and Lauwerys 1985, 1988; Lerman et al. 1983). The main site of methylation appears to be the liver, where the methylation process is mediated by enzymes that utilize S-adenosylmethionine as cosubstrate (Buchet and Lauwerys 1985, 1988). Under normal conditions, the availability of methyl donors (e.g., methionine, choline, cysteine) does not appear to be rate limiting in methylating capacity, either in humans (Buchet et al. 1982) or in animals (Buchet and Lauwerys 1987; Buchet et al. 1981a). However, severe dietary restriction of methyl donor intake can result in significant decreases in methylating capacity (Buchet and Lauwerys 1987; Vahter and Marafante 1987).

Arsenic methyltransferase and MMA methyltransferase activities have been purified to homogeneity from cytosol of rabbit liver (Zakharyan et al. 1995) and Rhesus monkey liver (Zakharyan et al. 1996). It

appears that a single protein (MW 60,000) catalyzes both activities. This activity transfers a methyl group from S-adenosylmethionine to As(+3) yielding MMA, which is then further methylated to DMA. Reduced glutathione is probably a co-factor *in vivo*, but other thiols can substitute *in vitro* (L-cysteine, dithiothreitol). The substrate saturation concentration for rabbit arsenite methyltransferase is 50 μM, for MMA methyltransferase it is 1,000 μM. The purified activity is specific for arsenite and MMA; selenite, selenate, selenide, and catechols do not serve as substrates.

Studies in mice indicate that exposure to arsenic does not induce arsenic methylation activity (Healy et al. 1998). Mice receiving up to 0.87 mg As/kg/day as sodium arsenate in drinking water for 91 days had the same arsenic methylating activity as unexposed controls. Distribution of activity was reported in this study. Specific activities were highest in testis (1.45 U/mg) followed by kidney (0.70 U/mg), liver (0.40 U/mg), and lung (0.20 U/mg). None were affected by arsenic exposure.

Since the methyl derivatives of arsenic appear to be less toxic than inorganic arsenic (see Section 2.2), and since methylation tends to result in lower tissue retention of inorganic arsenic (Marafante and Vahter 1984, 1986; Marafante et al. 1985; Vahter and Marafante 1987), the methylation process is usually viewed as a detoxification mechanism. Because methylation is an enzymic process, an important issue is the dose of arsenic that saturates the methylation capacity of an organism, resulting in a possible increased level of the more toxic As(+3) in tissues. Limited data from studies in humans suggest that methylation may begin to become limiting at doses of about 0.2–1 mg/day (0.003–0.015 mg/kg/day) (Buchet et al. 1981b; Marcus and Rispin 1988). However, these observations are relatively uncertain since they are based on data from only a few people, and the pattern of urinary excretion products in humans who ingested high (near lethal) oral doses or were exposed to elevated levels in the workplace is not much different from that in the general population (Lovell and Farmer 1985; Vahter 1986). Furthermore, the nutrient intakes reported by Engel and Receveur (1993) were sufficient to accommodate the body stores of methyl groups needed for arsenic biomethylation. At the highest arsenic level reported in the endemic area, the biomethylation process required only a few percent of the total daily methyl intake (Mushak and Crocetti 1995). Thus, the dose rate at which methylation capacity becomes saturated cannot be precisely defined with current data.

Organic arsenicals appear to undergo little metabolism. Humans who ingested a dose of MMA converted a small amount (about 13%) to DMA (Buchet et al. 1981a), and several studies in hamsters have noted the formation of low levels of the trimethyl derivative (trimethylarsine oxide, $(CH_3)_3AsO$) (Yamauchi and Yamamura 1984; Yamauchi et al. 1988). However, the methylarsenates are not demethylated to

inorganic arsenic either in humans (Buchet et al. 1981a; Marafante et al. 1987b) or in animals (rats and hamsters) (Stevens et al. 1977b; Yamauchi and Yamamura 1984).

2.3.4 Elimination and Excretion

2.3.4.1 Inhalation Exposure

As noted previously (see Section 2.3.1.1), urinary excretion of arsenic appears to account for 30–60% of the inhaled dose (Holland et al. 1959; Pinto et al. 1976; Vahter et al. 1986). Since the deposition fraction usually ranges from about 30 to 60% for most respirable particles (EPA 1989b), this suggests that nearly all arsenic that is deposited in the lung is excreted in the urine. The time course of excretion in humans exposed by inhalation has not been thoroughly investigated, but urinary arsenic levels in workers in a smelter rose within hours after they came to work on Monday and then fell over the weekend (Vahter et al. 1986). This implies that excretion is fairly rapid, and this is supported by intratracheal studies in rats (Rhoads and Sanders 1985) and hamsters (Marafante and Vahter 1987), where whole body clearance of administered arsenate or arsenite occurred with a half-time of 1 day or less. However, small amounts of arsenic may remain bound in the lung, and only be cleared with a half-time of several months (Rhoads and Sanders 1985).

No studies were located regarding the excretion of organic arsenicals by humans or animals after inhalation exposure. However, rats that were given a single intratracheal dose of DMA excreted about 60% in the urine and about 8% in the feces within 24 hours (Stevens et al. 1977b). This indicates that organic arsenicals are likely to be promptly excreted after inhalation exposure.

2.3.4.2 Oral Exposure

Direct measurements of arsenic excretion in humans who ingested known amounts of arsenite or arsenate indicate that very little is excreted in the feces (Bettley and O'Shea 1975), and that 45–85% is excreted in urine within 1–3 days (Buchet et al. 1981a; Crecelius 1977; Mappes 1977; Tam et al. 1979b). During lactation, a very small percent of ingested arsenic may also be excreted in the breast milk (Concha et al. 1998a). A similar pattern of urinary and fecal excretion is observed in hamsters (Marafante and Vahter 1987; Yamauchi and Yamamura 1985) and mice (Vahter and Norin 1980). Accordingly, whole body clearance is fairly rapid, with half-times of 40–60 hours in humans (Buchet et al. 1981b; Mappes 1977).

Clearance is even more rapid in mice and hamsters, with 90% removed in 2 days (Marafante and Vahter 1987; Vahter 1981; Vahter and Norin 1980).

Studies in humans indicate that ingested MMA and DMA are excreted mainly in the urine (75–85%), and this occurs mostly within 1 day (Buchet et al. 1981a; Marafante et al. 1987b). This is supported by studies in rats and hamsters, although in animals excretion is more evenly distributed between urine and feces (Marafante et al. 1987b; Stevens et al. 1977b; Yamauchi and Yamamura 1984; Yamauchi et al. 1988).

2.3.4.3 Dermal Exposure

No studies were located regarding excretion of inorganic arsenicals in humans or animals following dermal exposure. In rats, arsenic absorbed through the tail was excreted approximately equally in urine and feces, similar to the excretion pattern following oral exposure (Dutkiewicz 1977).

No studies were located regarding excretion of organic arsenicals in humans or animals following dermal exposure.

2.3.4.4 Other Routes of Exposure

Excretion of arsenate and arsenite following parenteral exposure of animals is similar to that seen following oral exposure. In rabbits and mice, urinary excretion within 8 hours usually accounts for about 50–80% of the dose (Maehashi and Murata 1986; Maiorino and Aposhian 1985; Vahter and Marafante 1983). Somewhat lower levels (30–40%) are excreted in the urine of marmoset monkeys (Vahter and Marafante 1985; Vahter et al. 1982), probably because of the absence of methylation in this species. Whole-body clearance studies in mice indicate that arsenate is over 65% removed within 24 hours, while arsenite is about 86% removed at 24 hours (Lindgren et al. 1982).

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

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of

potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

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

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

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

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994).

PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 2-5 shows a conceptualized representation of a PBPK model.

If PBPK models for arsenic 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.

PBPK models for arsenic are discussed below.

2.3.5.1 Summary of PBPK Models.

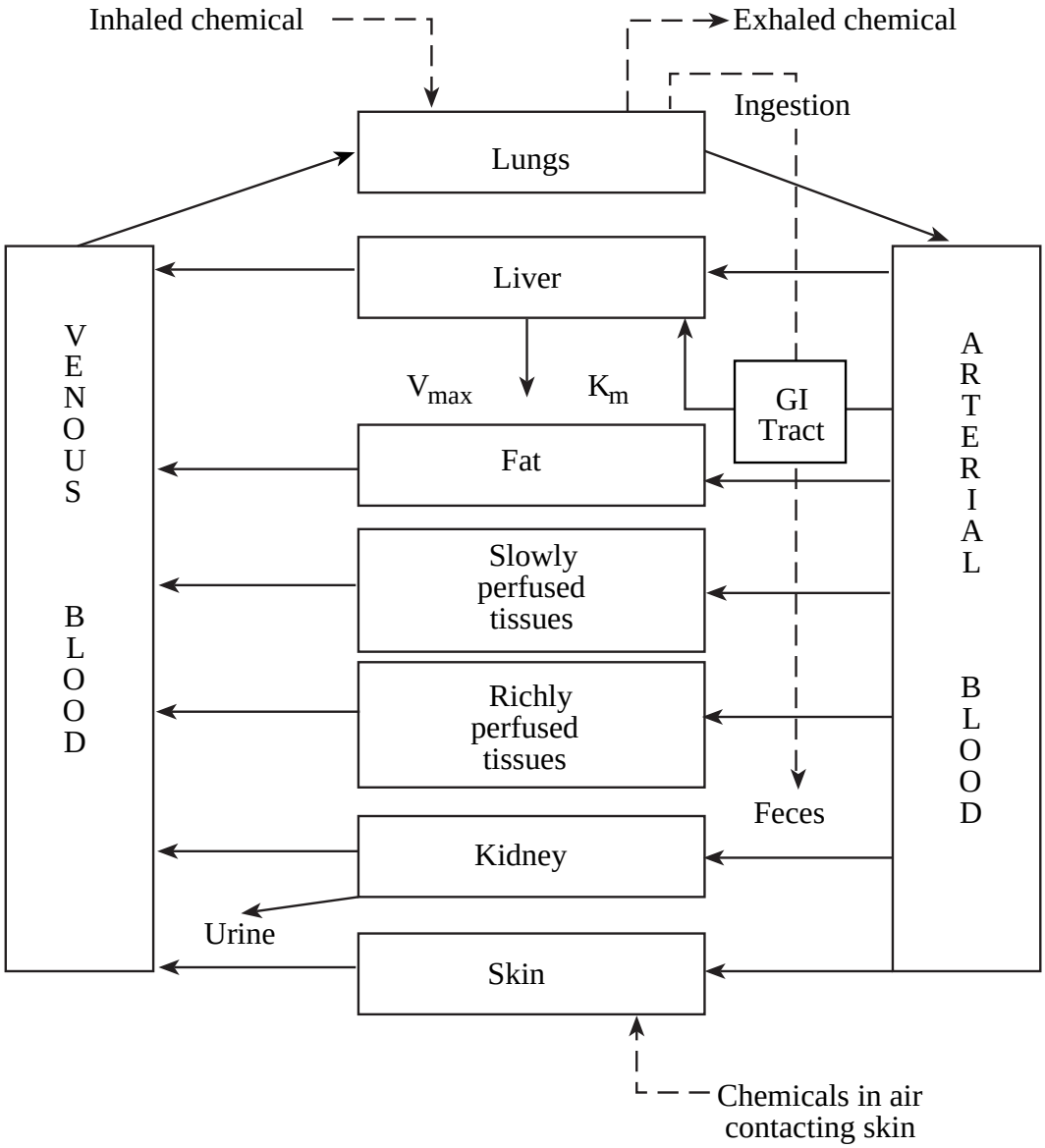
The Mann model (Mann et al. 1996a, 1996b),Yu model (Yu 1998a, 1998b), and Menzel model (Menzel et al. 1994) are the PBPK models for arsenic currently available. The Mann model simulates the absorption, distribution, metabolism, elimination, and excretion of As(+3), As(+5), MMA, and DMA after oral and inhalation exposure in hamsters, rabbits, and humans. The Yu model simulates the absorption, distribution, metabolism, elimination, and excretion of As(+3), As(+5), MMA, and DMA after oral exposure to inorganic arsenic in mice and rats. The Menzel model is a preliminary model that predicts internal organ burden of arsenic during specific oral exposures, simulating the metabolism, distribution to organs and binding to organs in mice, rats, and humans.

2.3.5.2 Arsenic PBPK Model Comparison.

The Mann model is a well-derived model, consisting of multiple compartments and metabolic processes, and modeling four chemical forms of arsenic (two organic and two inorganic), which has been validated using experimental data. The Yu model has more compartments than the Mann model, also models metabolism and fate of four forms of arsenic, and has likewise been validated using experimental data. The Menzel model is still preliminary and has not been validated.

Figure 2-5. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance

Source: adapted from Krishnan et al. 1994



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

2.3.5.3 Discussion of Models.

The Mann Model.

Risk assessment. The Mann model was not used for risk assessment.

Description of the model. The Mann model was initially developed to simulate oral, intratracheal, and intravenous exposure to arsenic in rabbits and hamsters (Mann et al. 1996a). In a companion paper, the model was expanded to include inhalation exposure and extrapolated and applied to humans (Mann et al. 1996b).

The model consists of six tissue compartments: blood, liver, kidneys, lungs, skin, and other tissues. The blood compartment is divided into plasma and red blood cell subcompartments, considered to be at equilibrium. Three routes of exposure are considered in the model. Oral exposure is considered to enter the liver from the gastrointestinal tract via first-order kinetics. Intratracheal exposure results in deposition into the pulmonary and tracheo-bronchial regions of the respiratory tract. Uptake into blood from the pulmonary region is considered to be via first order kinetics into plasma, uptake from the tracheo-bronchial is by both transfer into plasma and transport into the gastrointestinal tract. Intravenous injection results in a single bolus dose into the plasma compartment.

Metabolism in the model consists of oxidation/reduction and two methylation reactions. The oxidation/reduction of inorganic arsenic was modeled as a first order process in the plasma, with reduction also included in the kidneys. Methylation of As(+3) was modeled as a two-step process occurring in the liver according to Michaelis-Menton kinetics.

Most physiological parameters were derived by scaling to body weight (Lindstedt 1992). In cases where parameters were not available (absorption rates, tissue affinity, biotransformation), estimates were obtained by fitting. This was done by duplicating the initial conditions of published experiments in the model, varying the unknown parameters and comparing the results of the simulation to the reported results. Tissue affinity constants were estimated using reported arsenic levels in tissues at various times after exposure. Metabolic rate constants and absorption rate constants were estimated using data for excretion of arsenic metabolites in urine and feces. Figure 2-6 shows the animal model and Tables 2-6, 2-7, 2-8, and 2-9 provide the parameters used in the animal model.

Table 2-6. Parameters Used in the Mann PBPK Model for Animals

Physiological parameter	Rabbit (bw = 3.5 kg)	Hamster (bw = 0.100 kg)
Blood volume (mL)	253	7.0
Organ weight (g)		
Liver	121	4.8
Kidneys	25	1.2
Lungs	31	1.0
Skin	420	17.1
Organ volume (mL)		
Others	2,386	62.0
Lumen volume (mL)		
Stomach	15	0.5
Small intestine	20	0.6
Blood flow (mL/min)		
Cardiac output	556	38.3
Liver, hepatic	25	1.2
Liver, splanchic	98	6.0
Kidneys	100	7.0
Lungs	13	0.7
Skin	38	2.6
Others	282	20.8
Clearance (mL/minute)		
Glomerular Filtration Rate	10	0.6
Small intestine length (cm)	180	56.0
Total capillary surface area (cm^2)	93,835	2,681.0

Source: Mann et al. 1996a

bw = body weight; PBPK = physiologically based pharmacokinetic

Table 2-7. Tissue Affinity Constants (K_{ij}) Obtained for the Mann PBPK Model for Animals by Fitting for Rabbits and Hamsters

	K_{ij} (unitless)			
Tissue (*i*)	As(V)	As(III)	MMA	DMA
Liver	1	200	10	1
Kidneys	40	20	100	5
Lungs	1	1	1	20
Skin	1	60	50	1
Others	10	40	1	1

Source: Mann et al. 1996a

DMA = dimethyl arsinic acid; MMA = monomethyl arsonic acid; PBPK = physiologically based pharmacokinetic

Table 2-8. Metabolic Rate Constants for the Mann PBPK Model for Animals Obtained by Fitting for Rabbits and Hamsters

Oxidation/reduction	First order	Rabbit	Hamster
Reduction	(1/hour)	3000.00	100.00
Oxidation	(1/hour)	6000.00	400.00
Kidney reduction	(1/hour)	30.00	1.00
Methylation	Michaelis–Menten		
1st step	$K_{M_{MMA}}$ (µmol/mL)	0.05	0.12
	$V_{MAX_{MMA}}$ (µmol/mL• hour)	4.00	0.12
2nd step	$K_{M_{DMA}}$ (µmol/mL)	0.90	0.08
	$V_{MAX_{DMA}}$ (µmol/mL• hour)	1.50	0.12

Source: Mann et al. 1996a

PBPK = physiologically based pharmacokinetic

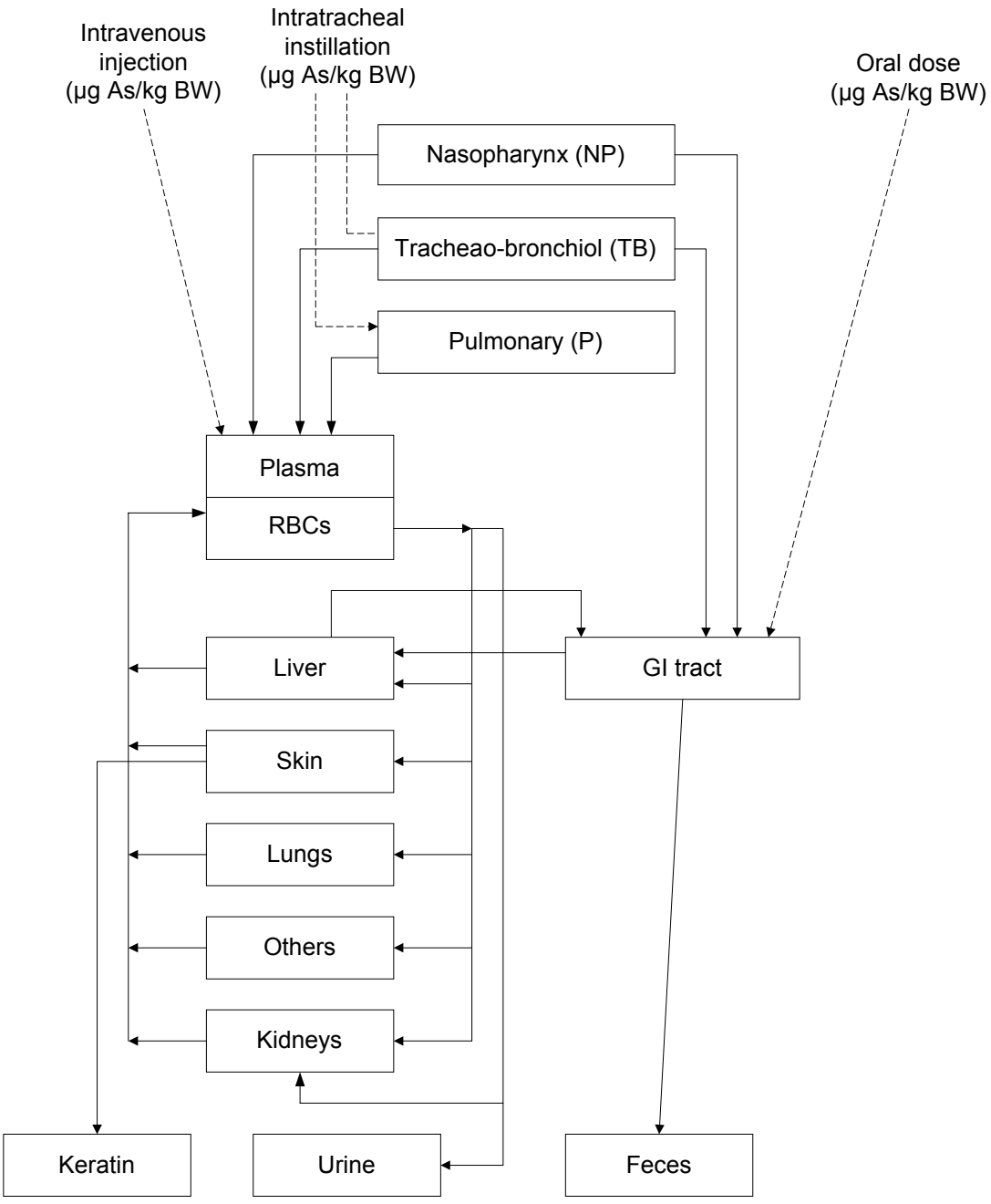
Table 2-9. Fitted Gastrointestinal Tract and Lung Absorption Half-time for the Hamster for the Mann PBPK Model

	Absorption, half-time (hour)	
Exposure As compound	Gastrointestinal tract	Lung
As(V)		
$Na_3(AsO_4)$	0.08	12
$Pb_3(AsO_4)$	0.39	690
As_2O_5	0.28	-
As(III)		
$NaAsO_2$	0.08	12
As_2S_3	0.48	12
As_2O_3	0.02	-
DMA	0.09	-

Source: Mann et al. 1996a

DMA = dimethyl arsenic acid; PBPK = physiologically based pharmacokinetic

Figure 2-6. Parameters Used in the Mann PBPK Model for Animals



Source: Mann et al. 1996b

The human model is similar to the animal models with adjustments for body weight and absorption and metabolic rates. A naso-pharynx compartment is included in the human model which was not present in the animal models. Penetration and deposition in the respiratory tract are based on the log-normal particle size distribution of the aerosol. Metabolic and absorption rate constants were fitted using experimental data on urinary excretion of arsenic following a single oral dose of As(+3) (Buchet et al. 1981a) or As(+5) (Tam et al. 1979b) in volunteers. The lung absorption rate constant was obtained by fitting the total urinary excretion of arsenic as predicted with the model to experimental data obtained from occupational exposure to arsenic trioxide (Offergelt et al. 1992). Figure 2-7 shows the human model, and Tables 2-10 and 2-11 provide the data and constants used in the human model.

Validation of the model. The model was generally successful in describing the disposition of an intravenous dose of sodium arsenate in rabbits over a 24-hour period (Marafante et al. 1985). Discrepancies included a 6–7-fold overestimation of levels in skin at 24 hours and underestimation of As(+5) in plasma in the hour following injection. A statistical assessment of how well the model fit the empirical data was not presented. In hamsters, the model was also generally predictive of oral and intratracheal exposures (Marafante and Vahter 1987). Generally, predictions were better for the exposures to As(+5) than for those to As(+3).

The human model was validated using data from studies of repeated oral intake of sodium arsenite in volunteers (Buchet et al. 1981b), occupational exposure to arsenic trioxide and elemental arsenic (Vahter et al. 1986), and community exposure to As(+5) via drinking water (Harrington et al. 1978; Valentine et al. 1979). Simulations were generally in good agreement with the experimental data.

Target tissues. Levels in skin were not well predicted by this model in animals; results for the lung were not presented. The human model was only used to predict urinary metabolites.

Species extrapolation. Species extrapolation was not attempted in this model. However, tissue affinities derived for the rabbit and hamster models were used in the human model.

Interroute extrapolation. Interroute extrapolation was not attempted in this model.

Table 2-10. Physiological Data Used in the Mann PBPK Model for Humans

Physiological parameter	Organ	Units	Human (bw = 70 kg)
Blood volume		mL	5,222
Organ weight	Liver	g	1,856
	Kidneys	g	314
	Lungs	g	584
	Skin	g	6,225
	Others	g	55,277
Lumen volume	Stomach	mL	274
	Small intestine	mL	393
Blood flow	Cardiac output	L/minute	5.29
	Liver, hepatic	L/minute	0.32
	Liver, splanchic	L/minute	1.02
	Kidneys	L/minute	0.95
	Lungs	L/minute	0.16
	Skin	L/minute	0.35
	Others	L/minute	2.49
Creatinine			
Male		g/day	1.7
Female		g/day	1.0
Clearance			
Glomerular Filtration Rate		mL/minute	156
Small intestine length		cm	481
Nasopharynx area		cm^2	177
Tracheobronchial area		cm^2	5,036
Pulmonary area		cm^2	712,471
Total capillary surface area		cm^2	$1,877x10^6$

Source: Mann et al. 1996b

bw = body weight; PBPK = physiologically based pharmacokinetic

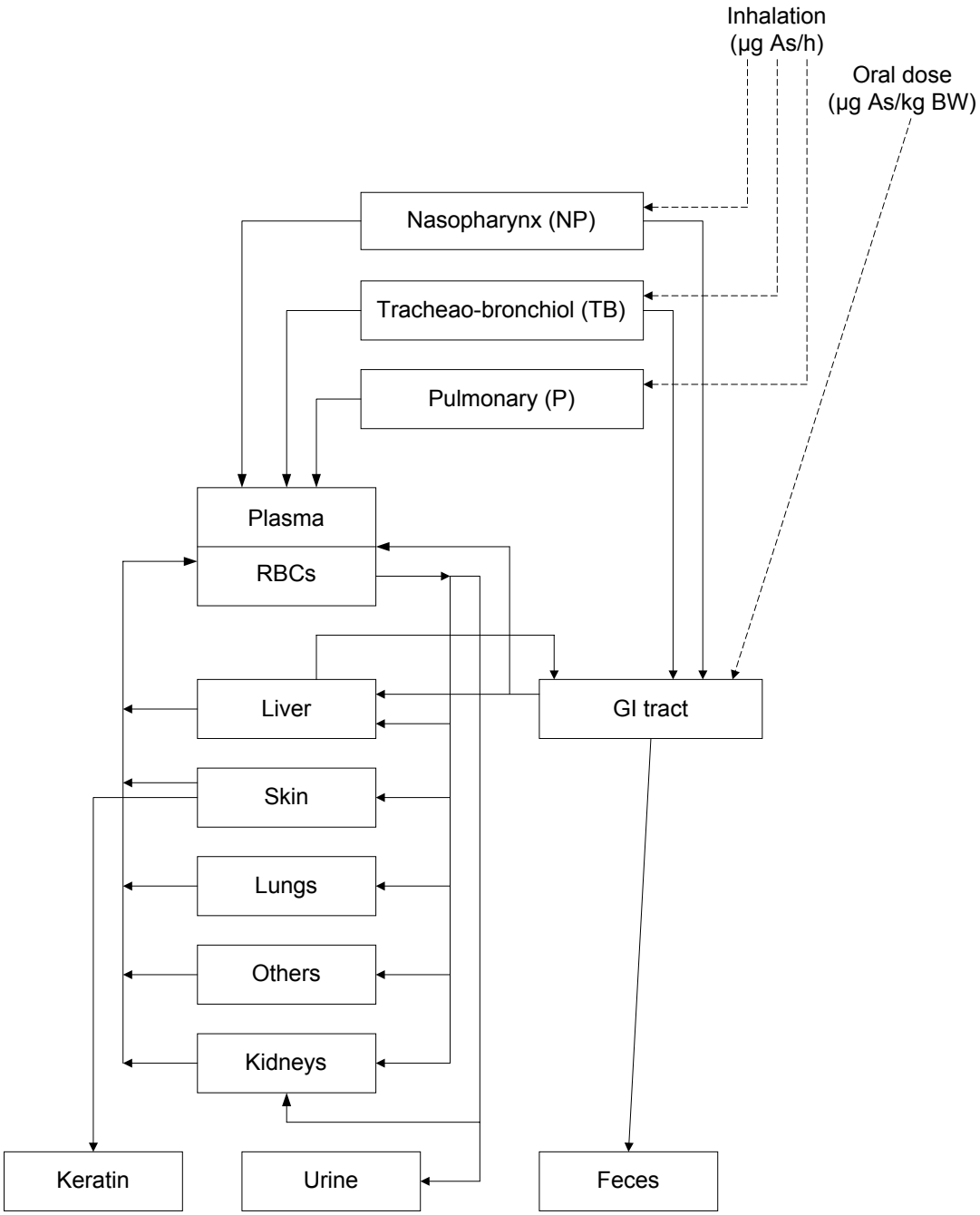
Table 2-11. Tissue Affinity Constants (K_{ij}) Obtained by Fitting the Mann PBPK Animal Model for Use with Humans

	K_{ij} (unitless)			
Tissue (*i*)	As(V)	As(III)	MMA	DMA
Liver	1	200	10	1
Kidneys	40	20	100	5
Lungs	1	1	1	20
Skin	1	60	50	1
Red blood cells	0.2	1.5	0.2	0.2
Others	10	40	1	1

Source: Mann et al. 1996b

DMA = dimethyl arsinic acid; MMA = monomethyl arsonic acid; PBPK = physiologically based pharmacokinetic

Figure 2-7. Parameters Used in the Mann PBPK Model for Humans



Source: Mann et al. 1996b

The Menzel Model.

Risk assessment. The Menzel model was not used for risk assessment.

Description of the model. The Menzel model was developed to simulate oral exposure to arsenic from drinking water and food. Inhalation of arsenic in the particulate phase or as arsine gas is not considered. The chemical species in drinking water is assumed to be As(+5).

The model consists of two sets of compartments: those in which the pools of arsenic are not influenced by blood perfusion, and those in which blood perfusion does determine arsenic burden. The former set of compartments includes the gut, feces, hair, bladder, and urine. The latter set of compartments included lung, liver, fat, skin, kidney, and other tissues. Oral exposure is considered to enter the liver from the gastrointestinal tract.

The model followed that of Anderson and coworkers (Anderson et al. 1987; Ramsey and Anderson 1984). Data from mice were used to test predictions of absorption. Excretion is considered to be rapid and complete into the urine, with no reabsorption from the kidney. Fecal arsenic content accounts for unabsorbed arsenic excreted in the bile, and complex arsenic species from food. Metabolism includes reduction by glutathione and methylation. Arsenic accumulation in the skin, hair and nails was included by assuming that arsenic binds irreversibly to protein sulfide groups in hair and nails.

Validation of the model. The model was preliminary and has not been validated.

Target tissues. Target tissues have not yet been modeled.

Species extrapolation. Species extrapolation was not attempted in this model.

Interroute extrapolation. Interroute extrapolation was not attempted in this model.

The Yu Model.

Risk assessment. The Yu model was not used for risk assessment.

Description of the model. The Yu model was developed to simulate oral exposure to arsenic in mice and rats (Yu 1998a, 1998b, 1999). Inhalation of arsenic in the particulate phase or as arsine gas is not considered. As(+3), As(+5), MMA, and DMA were all considered in the model, though the movements of MMA and DMA were not considered.

The model consists of eight tissue compartments: intestine, skin, muscle, fat, kidney, liver, lung, and vessel-rich group (VRG, e.g., brain). Only oral exposure was considered. Absorption is based on absorption to the stomach, which then passes the arsenic to the gastrointestinal tract. From the gastrointestinal tract, arsenic is either transferred to the blood or excreted in the feces.

The physiological parameters for the model were obtained from published values in the literature. Tissue/blood partition coefficients were based on the postmortem blood and tissue concentrations from a fatal human poisoning case study (Saady et al. 1989). Tissue volumes and blood flow rates were based on published values from a number of sources (EPA 1988f; Reitz et al. 1990). Absorption and excretion rate constants were based on experimental observations of blood concentrations and urinary and fecal excretion following oral administration of inorganic arsenic (Odanaka et al. 1980; Pomroy et al. 1980). Metabolic rate constants for the methylation and dimethylation of inorganic arsenic were also based on experimental observations (Buchet et al. 1981a; Crecelius 1977). Figure 2-8 shows the model and Table 2-12 provide the parameters used for each species.

Validation of the model. The model was generally successful at predicting the urinary excretion 48 hours after administration of 5 mg/kg inorganic arsenic in both rats and mice. After 48 hours, the observed/predicted ratios associated with excreted doses ranged from 0.78 to 1.11 for the mouse and 0.85 to 0.93 for the rat. However, the model overpredicted the amount of inorganic arsenic found in the feces of both mice at 24 and 48 hours, and overpredicted the amount of DMA formed by exposed mice at 48 hours. In rats, the model overestimated the urinary and fecal excretion of inorganic arsenic at 24 hours postexposure, though at 48 hours, measured values all fell within the predicted ranges. The ability of the model to predict tissue burdens was not compared to actual data.

Target tissues. Model predictions of tissue burdens were not compared to actual data. The model accurately predicted, with a few exceptions, the urinary and fecal excretion of inorganic arsenic and its metabolites in rats and mice.

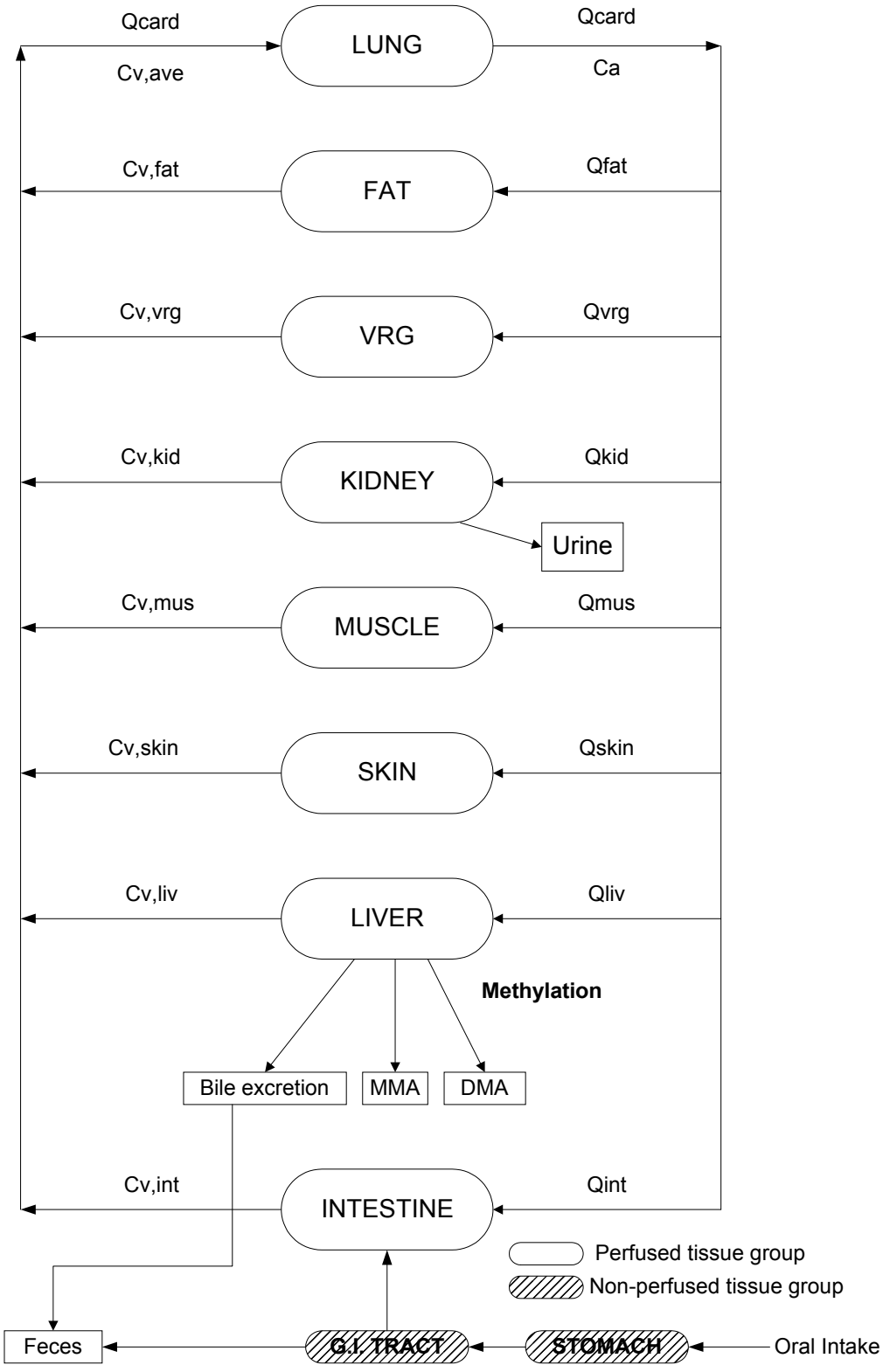
Table 2-12. Parameters Used in the Yu PBPK Model

	Mouse	Rat
Partition coefficients		
Intestine	6.0	6.0
Skin	5.0	5.0
VRG	6.0	6.0
Muscle	5.0	10.0
Fat	-	0.5
Kidney	8.5	7.5
Liver	10.0	10.0
Lung	4.0	4.0
Blood flow rate (mL/hour)		
Intestine	100	528
Skin	7.68	37.8
VRG	157	960
Muscle	153	1260
Fat	-	253.2
Kidney	255	255
Liver	255	1260
Tissue volume (mL)		
Intestine	1.94	6.9
Skin	1.83	15.4
VRG	0.81	23.0
Muscle	19.9	162
Fat	-	14.5
Kidney	0.484	1.63
Liver	1.67	5.82
Lung	0.124	1.0
Metabolism constants		
$Vmax_{(MMA)}$ (µmol/hour)	0.45	0.15
$Vmax_{(DMA)}$ (µmol/hour)	0.375	0.06
$Km_{(MMA)}$(µmol/hour)	1.0	0.2
$Km_{(DMA)}$(µmol/hour)	0.2	0.2
First-order rate constants		
K_{SI}($hour^{-1}$)	0.3	0.3
K_{AI}($hour^{-1}$)	1.5	3.6
K_{fecal}($hour^{-1}$)	0.33	0.048
$K_{urinary}$($hour^{-1}$)	1.32	0.9
$K_{biliary}$($hour^{-1}$)	0.33	0.3

Values taken from Yu 1998a, 1998b.

PBPK = physiologically based pharmacokinetic

Figure 2-8. Parameters Used in the Yu PBPK Model for Animals



Species extrapolation. Species extrapolation beyond rats and mice was not attempted using this model.

Interroute extrapolation. Interroute extrapolation was not attempted using this model.

2.4 MECHANISMS OF ACTION

2.4.1 Pharmacokinetic Mechanisms

Arsenic absorption depends on its chemical form. In humans, As(+3), As(+5), MMA, and DMA are orally absorbed $80%. Arsenic is also easily absorbed via inhalation. Absorption appears to be by passive diffusion in humans and mice, although there is evidence for a saturable carrier-mediated transport process for arsenate in rats (Gonzalez et al. 1995). Dermal absorption appears to be much less than by the oral or inhalation routes. Bioavailability of arsenic from soil appears to be lower via the oral route than it is for sodium salts of arsenic. Arsenic in soil may form water insoluble compounds (e.g., sulfides) which are poorly absorbed.

Arsenic and its metabolites distribute to all organs in the body; preferential distribution has not been observed in human tissues at autopsy or in experiments with animal species other than rat (in which arsenic is concentrated in red blood cells). Since the liver is a major site for the methylation of inorganic arsenic, a “first-pass” effect is possible after gastrointestinal absorption; however, this has not been investigated in animal models.

Arsenic and its metabolites are largely excreted via the renal route. This excretion mechanism is not likely to be saturated within the dose range expected from human exposure. Excretion can also occur via feces after oral exposure; a minor excretion pathway is nails and hair. The methylation of inorganic arsenic is the major detoxification pathway. The proportion of metabolites recovered in urine [As(+3), As(+5), MMA, DMA] are roughly consistent in humans regardless of the exposure scenario. However, interindividual variation is great enough that it cannot be determined if capacity limitation may occur in some individuals.

The manifestation of arsenic toxicity depends on dose and duration of exposure. Single oral doses in the range of 20 mg As/kg and higher have caused death in humans. Doses as low as 0.05 mg As/kg/day over longer periods (weeks to months) have caused gastrointestinal, hematological, hepatic, dermal, and

neurological effects. These effects appear to be a result of direct cytotoxicity. Long-term exposure (years) to drinking water at levels as low as 0.001 mg As/kg/day have been associated with skin diseases and skin, bladder, kidney, and liver cancer. Long-term inhalation exposure to arsenic has also been associated with lung cancer at air levels as low as 0.05–0.07 mg/m^3. It is not clear at this time why long-term toxicity is different between the oral and inhalation routes, given that arsenic is easily absorbed into the systemic circulation by both routes.

Studies in mice and rats have shown that arsenic compounds induce metallothionein, a metal-binding protein thought to detoxify cadmium and other heavy metals, *in vivo* (Albores et al. 1992; Hochadel and Waalkes 1997; Kreppel et al. 1993; Maitani et al. 1987a). The potency of arsenic compounds in inducing metallothionein parallels their toxicity (i.e., As(+3) > As(+5) > MMA > DMA). For cadmium, it is thought that metallothionein binds the metal, making it biologically inactive. For arsenic, however, only a small percentage of the administered metal is actually bound to metallothionein (Albores et al. 1992; Kreppel et al. 1994; Maitani et al. 1987a). *In vitro* studies have shown that affinity of arsenic for metallothionein is much lower than that of cadmium or zinc (Waalkes et al. 1984). It has been proposed that metallothionein might protect against arsenic toxicity by acting as an antioxidant against oxidative injury produced by arsenic (NRC 1999).

2.4.2 Mechanisms of Toxicity

Effect of Metabolism on Toxicity. The effect of metabolism on toxicity appears to depend on dose. In relatively high oral exposures ($0.05 mg/kg/day), it is likely that methylation capacity is not adequate to prevent cytotoxic levels of As(+3) from reaching tissues. At lower long-term doses, which have been associated with cancer, the relationship between metabolism and toxicity is the object of debate. The demand of arsenic on cellular methylating capacity (particularly the co-factor S-adenosylmethionine) may lower the efficiency of other cellular methyltransferases. These effects on DNA methylating activity are discussed below.

Target Organ Toxicity. Relatively high-dose acute- and intermediate-duration toxicity appears to be the result of arsenic cytotoxicity. Reduced inorganic arsenic [As(+3)] reacts strongly with sulfhydryl groups in proteins and inactivates many enzymes. A particular target in the cell is the mitochondria, which accumulates arsenic (Goyer 1991). Arsenic inhibits succinic dehydrogenase activity and can uncouple oxidative phosphorylation; the resulting fall in ATP levels affects virtually all cellular functions (Na+/K+ balance, protein synthesis, etc.).

Carcinogenesis. The EPA and the International Agency for Research on Cancer (IARC) classify arsenic as a carcinogen for which there is sufficient epidemiological evidence to support a causal relationship between exposure to arsenic and skin cancer. Unlike the large majority of substances considered as human carcinogens based on epidemiological evidence, arsenic alone will not induce cancer in rodent models. The genotoxicity database for arsenic indicates that it does not induce point mutations or DNA adducts, but chromosomal aberrations and sister chromatid exchanges have been reported. Arsenic can also potentiate mutagenicity observed with other chemicals. This potentiation may be the result of direct interference by arsenic with DNA repair processes, perhaps by inhibiting DNA ligase (Li and Rossman 1989). Finally, arsenic can also induce DNA amplification (Lee et al. 1988).

It has been hypothesized that methylation changes in genes or their control regions can lead to altered gene expression, and potentially, carcinogenesis (Baylin et al. 1998; Costa 1995). Effects of arsenic on DNA methylation have been studied in two model systems. In the first, arsenite exposure in the human lung adenocarcinoma cell line A549 resulted in hypermethylation of cytosine in the promoter region of the tumor suppressor gene p53 (Mass and Wang 1997). In the second, hypomethylation throughout the genome was found in a rat liver cell line (TRL 1215) that had been exposed to submicromolar sodium arsenite for 18 weeks; these cells exhibited aberrant gene expression and had undergone malignant transformation, as demonstrated by the induction of tumors when injected into Nude mice (Zhao et al. 1997).

The tissue-specificity of arsenic carcinogenicity in humans is being studied in primary human epidermal keratinocytes (Germolec et al. 1997a). Low micromolar concentrations of sodium arsenite resulted in neoplasia accompanied by increased mRNA transcripts and secretion of growth factors including granulocyte macrophage-colony stimulating factor (GM-CSF), transforming growth factor alpha (TGF-α), and the cytokine tumor necrosis factor alpha (TNF-α). Arsenic in drinking water also increased the number of skin papillomas in transgenic mice in which dermal application of phorbol esters induces papillomas (genetically initiated mice). These results support a hypothesis that chronic low-level exposure to arsenic stimulates keratinocyte secretion of growth factors, the resulting increased cellular division (and concomitant DNA replication) allows greater opportunities for genetic damage to occur.

2.4.3 Animal-to-Human Extrapolations

The usefulness of animal models for toxicity studies with arsenic is limited by two major factors. First and most importantly, no animal model exists for the health effect of greatest concern for human

exposure: carcinogenicity in skin and other organs after oral exposure. Second, the pattern of metabolism in humans (significant excretion of the methylated forms of arsenic) is unlike most other mammalian species (the rabbit may be an exception). The ratios of inorganic to organic arsenic excreted also vary between species. The rat sequesters arsenic in its erythrocytes and is not a suitable model for human toxicity.

2.5 RELEVANCE TO PUBLIC HEALTH

Overview.

Arsenic is a potent toxicant that may exist in several valence states and in a number of inorganic and organic forms. Most cases of arsenic-induced toxicity in humans are due to exposure to inorganic arsenic, and there is an extensive database on the human health effects of the common arsenic oxides and oxyacids. Although there may be some differences in the potency of different chemical forms (e.g., arsenites tend to be somewhat more toxic than arsenates), these differences are usually minor and are not focused on in this profile.

Exposures of humans near hazardous waste sites could involve inhalation of arsenic dusts in air, ingestion of arsenic in water, food, or soil, or dermal contact with contaminated soil or water. By the inhalation route, the effect of greatest public health concern is increased risk of lung cancer, although respiratory irritation, nausea, and skin effects may also occur. As summarized in Table 2-1 and Figure 2-1 in Section 2.2.1, there are only a few quantitative data on noncancer effects in humans exposed to inorganic arsenic by the inhalation route. However, it appears that such effects are unlikely below a concentration of about 0.1–1.0 mg As/m^3.

The diet is usually the predominant source of exposure for the general population. The effects most likely to be of human health concern from ingestion of arsenic are gastrointestinal irritation, peripheral neuropathy, vascular lesions, anemia, a group of skin diseases, including skin cancer, and other cancers of the internal organs including bladder, kidney, liver, and lung cancer. As summarized in Table 2-3 and Figure 2-3 in Section 2.2.2, most of the noncancer effects tend to occur at similar oral exposure levels, indicating that the dose-response curves for these effects are similar. For acute and intermediate exposures, most reported LOAEL values are 0.05 mg As/kg/day or higher (see Figure 2-3). However, these data are mainly from case reports of poisoning episodes, so it is likely that lower doses could also produce the characteristic signs of acute arsenic toxicity. Chronic LOAELs are as low as 0.001 mg

As/kg/day and chronic NOAEL values are as low as 0.0004 mg As/kg/day (see Figure 2-3). Based on these data, the calculated provisional acute oral MRL is 0.005 mg/kg/day and the calculated chronic oral MRL is 0.0003 mg As/kg/day.

Relatively little information is available on effects due to direct dermal contact with inorganic arsenicals, but several studies indicate the chief effect is local irritation and dermatitis, with little risk of other adverse effects.

Humans may also be exposed to a variety of organic arsenicals (mainly methyl and phenyl derivatives of arsenic acid), since these are widely used in agriculture. Although human health effects data are sparse, it is generally considered that organic arsenicals are substantially less toxic than the inorganic forms. However, available data (mainly from animal studies) make clear that adequate doses of the methyl and phenyl arsenates can produce adverse health effects that resemble those of the inorganic arsenicals, and so the possibility of health risks from the organic arsenicals should not be disregarded.

Presented below are more detailed descriptions and discussions of the characteristic adverse effects of the inorganic and organic arsenicals most likely to be of concern to humans. These evaluations focus on human health effects data wherever possible, since most studies in animals suggest that animals are less sensitive to arsenic than humans. Animal data are presented when human data are lacking, but these data should be extrapolated to humans only with caution.

Issues relevant to children are explicitly discussed in Sections 2.7 Children's Susceptibility and Section 5.6 Exposures of Children.

Minimal Risk Levels for Arsenic.

Inhalation MRLs.

No inhalation MRLs were derived for arsenic.

Oral MRLs.

- A provisional MRL of 0.005 mg/kg/day has been derived for acute-duration (14 days or less) oral exposure to arsenic.

Mizuta et al. (1956) summarized findings from 220 poisoning cases associated with an episode of arsenic contamination of soy sauce in Japan. The soy sauce was contaminated with approximately 0.1 mg As/mL, probably as calcium arsenate. Arsenic intake in the cases was estimated by the researchers to be 3 mg/day (0.05 mg/kg/day, assuming 55 kg average body weight for this Asian population). The duration of exposure was 2–3 weeks in most cases. The primary symptoms were edema of the face, and gastrointestinal and upper respiratory symptoms initially, followed by skin lesions and neuropathy in some patients. Other effects included mild anemia and leukopenia, mild degenerative liver lesions and hepatic dysfunction, abnormal electrocardiogram, and ocular lesions. For derivation of the provisional acute oral MRL, facial edema and gastrointestinal symptoms (nausea, vomiting, diarrhea), which were characteristic of the initial poisoning and then subsided, were considered to be the critical effects. The provisional MRL of 0.005 mg As/kg/day was calculated by applying an uncertainty factor of 10 (10 for use of a LOAEL and 1 for intrahuman variability) to the LOAEL of 0.05 mg As/kg/day (see Appendix A for MRL worksheets). The MRL is considered provisional because the gastrointestinal effects (nausea, vomiting, diarrhea, and occult blood in feces and gastric and duodenal juice) are serious and because serious neurological (hypesthesia in legs, abnormal patellar reflex) and cardiovascular (abnormal electrocardiogram) effects also occurred at the same dose. Although it is not customary to base an MRL on a serious LOAEL, public health concerns regarding arsenic suggested that a provisional value derived from these data would be useful for the general public.

- An MRL of 0.0003 mg/kg/day has been derived for chronic-duration (365 days or more) oral exposure to arsenic.

Tseng et al. (1968) and Tseng (1977) investigated the incidence of Blackfoot disease and dermal lesions (hyperkeratosis and hyperpigmentation) in a large number of poor farmers (both male and female) exposed to high levels of arsenic in well water in Taiwan. A control group consisting of 17,000 people, including one group in which arsenic exposure was “undetermined” and included those villages where arsenic-contaminated wells were no longer used or the level could not be classified, and a control population of 7,500 people who consumed water from wells almost free of arsenic (0.001–0.017 ppm) was also examined. The authors stated that the incidence of dermal lesions increased with dose, but individual doses were not provided. However, incidence data were provided based on stratification of the exposed population into low (<300 µg/L), medium (300–600 µg/L), or high (>600 µg/L) exposure levels. Doses were calculated from group mean arsenic concentrations in well water, assuming the intake parameters described by Abernathy et al. (1989). Accordingly, the control, low-, medium-, and high-exposure levels correspond to doses of 0.0008, 0.014, 0.038, and 0.065 mg As/kg/day, respectively. The

NOAEL identified by Tseng (1977) (0.0008 mg As/kg/day) was limited by the fact that the majority of the population was less than 20 years of age and the incidence of skin lesions increased as a function of age, and because the estimates of water intake and dietary arsenic intake are highly uncertain. Schoof et al. (1998) estimated that dietary intakes of arsenic from rice and yams may have been 15–211 µg/day (mean=61 µg/day), based on arsenic analyses of foods collected in Taiwan in 1993–1995. Use of the 50 µg/day estimate would result in an approximate doubling of the NOAEL (0.016 mg/kg/day) (see Appendix A for MRL worksheets).

No intermediate-duration MRL was derived due to lack of suitable studies.

Death. There have been many reported cases of death in humans due to ingestion of inorganic arsenicals. Acute lethality is usually attributable to cardiopulmonary collapse (Levin-Scherz et al. 1987; Saady et al. 1989), while delayed lethality results from failure of one or more of the many tissues injured by arsenic (Campbell and Alvarez 1989). Estimates of the minimum lethal oral dose in humans range from 1 to 3 mg As/kg/day (Armstrong et al. 1984; Holland 1904; Vallee et al. 1960), although there may be considerable variation between individuals. The lowest lethal level in an animal study was 1.5 mg As/kg/day in pregnant rabbits dosed repeatedly throughout gestation. No cases were located regarding death in humans from inhalation exposure to inorganic arsenicals. The reason for this apparent route specificity is not clear, but might simply be due to lower exposure levels, or perhaps to toxicokinetic differences in exposure rate or arsenic metabolism. Dermal exposure to inorganic arsenicals has not caused lethality in humans, presumably because dermal absorption is very limited.

No cases of death in humans were located that are attributable to exposure to organic arsenicals, but studies in animals show that ingestion or inhalation of organic arsenicals (DMA, MMA, roxarsone) may be lethal. Fatal doses by the inhalation route are so high (above 2,000 mg As/m^3) (Stevens et al. 1979) as to be of no practical concern, while most oral and parenteral lethal doses range from 15 to 960 mg As/kg/day, depending on the compound and the animal species (Jaghabir et al. 1988; Kaise et al. 1989; NTP 1989b; Rogers et al. 1981; Stevens et al. 1979).

Systemic Effects

Respiratory Effects. Inhalation of inorganic arsenic dusts (usually containing mainly arsenic trioxide) is irritating to the nose, throat, and lungs, and can lead to laryngitis, bronchitis, and rhinitis (Dunlap 1921; Lundgren 1954; Morton and Caron 1989; Pinto and McGill 1953). However, chronic functional

impairment of respiration is not usually observed even in workers exposed to high levels of arsenic trioxide in air (Perry et al. 1948). Effects on the lung may actually be more pronounced following high-dose (i.e., near-lethal) oral exposure, where edema and hemorrhagic lesions have been noted (Campbell and Alvarez 1989; Civantos et al. 1995; Fincher and Koerker 1987; Levin-Scherz et al. 1987; Moore et al. 1994; Quatrehomme et al. 1992). It seems possible that this is due mainly to an effect of ingested arsenic on pulmonary blood vessels rather than on alveolar cells, but this is not known with certainty. In general, respiratory effects have not been widely associated with repeated oral ingestion of low arsenic doses. Nevertheless, a few studies have reported minor respiratory symptoms, such as cough, sputum, rhinorrhea, and sore throat, in people with repeated oral exposure to 0.03–0.05 mg As/kg/day (Ahmad et al. 1997; Mizuta et al. 1956).

The effects of organic arsenicals on the respiratory tract have not been well studied. There are no data by any route from human studies, but acute respiratory distress and lung injury have been reported in mice that inhaled very high levels of DMA (Stevens et al. 1979). Since only high exposures were investigated, it is not possible to compare the relative irritancy and respiratory toxicity of the organic and inorganic arsenicals.

Cardiovascular Effects. Several studies of smelter workers have reported that chronic exposure to arsenic trioxide may increase the risk of dying from cardiovascular disease (Axelson et al. 1978; Jensen and Hansen 1998; Lee-Feldstein 1983; Wall 1980). However, other confounding factors may have predisposed these workers to cardiovascular disease (i.e., lead, cigarette smoking). High oral doses of inorganic arsenic can lead to marked cardiac arrhythmias and altered electrocardiograms in humans (e.g., Glazener et al. 1968; Little et al. 1990). In severe cases, this can lead to premature ventricular contractions and ventricular tachycardia that require medical intervention (Goldsmith and From 1986) or may even result in death (Hall and Harruff 1989).

Chronic oral exposure to lower levels of inorganic arsenic can also result in serious damage to the vascular system. The most extreme manifestation of this is "Blackfoot disease," a progressive loss of circulation in the fingers and toes that ultimately leads to gangrene (Chen et al. 1988b; Chi and Blackwell 1968; Tseng et al. 1968, 1995). This disease has only been reported in one area of Taiwan, and it seems likely that other factors (e.g., fluorescent humic substances in the water) may contribute to the severity of the effect besides the elevated level of arsenic intake (Ko 1986; Lu et al. 1990; Yu et al. 1984). Symptoms of peripheral vascular disease, including Raynaud’s disease, and cyanosis and gangrene of the fingers and toes, which may represent less severe manifestations of what has become known as Blackfoot

disease, have been reported in other populations. These include populations in Bangledesh (Biswas et al. 1998), Mexico (Cebrian et al. 1983), and Chile (Borgono and Greiber 1972; Zaldivar 1977) that were exposed to high concentrations of arsenic in drinking water; wine vinters in Germany who ingested grape beverages that had a high concentration of arsenic (Roth 1957); and workers who were exposed to arsenic by the inhalation route (Lagerkvist et al. 1986, 1988).

Possible myocardial or vascular effects have not been investigated for the organic arsenicals, either in humans or animals.

Gastrointestinal Effects. Nausea, vomiting, and diarrhea are very common symptoms in humans following oral exposure to inorganic arsenicals, both after acute high-dose exposure (e.g., Fincher and Koerker 1987; Levin-Scherz et al. 1987; Lugo et al. 1969; Moore et al. 1994) and after repeated exposure to lower doses (e.g., Borgono and Greiber 1972; Cebrian et al. 1983; Franzblau and Lilis 1989; Mizuta et al. 1956). These effects are likely due mainly to a direct irritation of the gastrointestinal mucosa. Similar effects have also been observed following intermediate- or chronic-duration inhalation exposure (Beckett et al. 1986; Ide and Bullough 1988; Morton and Caron 1989), presumably because of the transfer of inhaled particulates from the respiratory tree to the stomach via mucociliary clearance. By either route, gastrointestinal symptoms usually wane within several days after exposure ceases (Mizuta et al. 1956). The provisional acute oral MRL of 0.005 mg/kg/day for inorganic arsenic was based in part on gastrointestinal irritation symptoms in people exposed by consumption of tainted soy sauce (Mizuta et al. 1956).

The effects of organic arsenicals on the gastrointestinal tract have not been as thoroughly investigated. No reports were located of gastrointestinal complaints in humans exposed to organic arsenicals, but inhalation exposure of rats to high doses of DMA can cause diarrhea (Stevens et al. 1979), and oral exposure of rabbits to MMA can cause intestinal irritation and weakening of the intestinal wall (Jaghabir et al. 1989). These data suggest that the organic arsenicals are capable of producing gastrointestinal effects similar to the inorganic arsenicals, but the data are too sparse to make quantitative comparisons.

Hematological Effects. Anemia is often observed in humans exposed to arsenic by the oral route (e.g., Armstrong et al. 1984; Glazener et al. 1968; Mizuta et al. 1956; Westhoff et al. 1975). This is probably due mainly to a toxic effect on the erythropoietic cells of bone marrow (Franzblau and Lilis 1989; Lerman et al. 1980; Westhoff et al. 1975), although increased hemolysis may also contribute (Goldsmith and From 1986; Kyle and Pease 1965). Leukopenia is also common in cases of oral exposure to inorganic

arsenicals (e.g., Armstrong et al. 1984; Franzblau and Lilis 1989; Kyle and Pease 1965). Similar depression of red or white blood cells has not been reported in workers exposed by the inhalation route (e.g., Beckett et al. 1986; Bolla-Wilson and Bleecker 1987; Ide and Bullough 1988; Morton and Caron 1989). As discussed above, the reason for this is not clear but may be simply a function of dose.

Information on possible hematological effects of organic arsenicals is sparse. No effects were observed in humans exposed to arsanilic acid (Watrous and McCaughey 1945), and no effects were detected in animals exposed to MMA, DMA, or roxarsone (NTP 1989b; Prukop and Savage 1986; Siewicki 1981). These data suggest that the organic arsenicals have low hematotoxicity, but the data are too limited to draw firm conclusions, particularly for humans.

Hepatic Effects. Oral exposure of humans to inorganic arsenicals often produce a swollen and tender liver (e.g., Chakraborty and Saha 1987; Guha Mazumder et al. 1988; Mizuta et al. 1956; Silver and Wainman 1952; Wade and Frazer 1953). Although large serum enzyme changes indicating hepatotoxicity have been found in some acute poisoning cases (Armstrong et al. 1984; Hantson et al. 1996; Kamijo et al. 1998; Levin-Scherz et al. 1987; Quatrehomme et al. 1992), there is usually only marginal evidence of hepatic cell injury with longer-term exposure to lower doses (Franzblau and Lilis 1989; Hernandez-Zavala et al. 1998) . Histological examination suggests that the principal lesion is a portal tract fibrosis and cirrhosis that results in portal hypertension (Franklin et al. 1950; Guha Mazumder et al. 1988; Morris et al. 1974; Szuler et al. 1979). Thus, the hepatic effects may be largely vascular in origin. Similar hepatic effects have not been noted in workers exposed to inorganic arsenic by the inhalation route (Bolla-Wilson and Bleecker 1987; Ide and Bullough 1988). However, too few human subjects have been studied to draw firm conclusions.

No information was located on hepatotoxic effects of organic arsenicals in humans, although some mild effects on liver weight and histological appearance have been detected in rats and mice given repeated oral doses of roxarsone (NTP 1989b) and rabbits given MMA (Jaghabir et al. 1989). These data are too limited to judge whether the organic arsenicals act on the liver similarly to inorganic arsenic.

Renal Effects. Signs of renal injury are usually mild or absent in cases of humans exposed to inorganic arsenic either by the oral route (Franzblau and Lilis 1989; Jenkins 1966; Kersjes et al. 1987; Mizuta et al. 1956; Silver and Wainman 1952) or by the inhalation route (Bolla-Wilson and Bleecker 1987; Ide and Bullough 1988). Acute renal failure in some bolus poisoning episodes (e.g., Fincher and Koerker 1987; Goebel et al. 1990; Levin-Scherz et al. 1987; Lugo et al. 1969; Moore et al. 1994) is probably a result of

fluid imbalances or vascular injury (Rosenberg 1974; Zaldivar 1974). These observations suggest that the kidney is relatively less sensitive to inorganic arsenic than other systemic target tissues, and that renal effects are unlikely to be of major human health concern.

No information was located on renal effects of organic arsenicals in humans, but histological signs of tubular damage have been noted in rats given repeated oral doses of roxarsone (NTP 1989b) and in rabbits given repeated oral doses of MMA (Jaghabir et al. 1989). This suggests that the organic arsenicals may have limited nephrotoxicity, but it is difficult to judge the significance of these observation for humans exposed to organic arsenicals.

Dermal Effects. Perhaps the single most common and characteristic sign of exposure to inorganic arsenic is a triad of dermatological manifestations, including hyperkeratinization of the skin (especially on the palms and soles), formation of multiple hyperkeratinized corns or warts, and hyperpigmentation of the skin with interspersed spots of hypopigmentation. One or more of these effects have been noted in numerous studies of intermediate or chronic oral exposure to inorganic arsenic (e.g., Borgono and Greiber 1972; Cebrian et al. 1983; Chakraborty and Saha 1987; Guha Mazumder et al. 1988; Nagai et al. 1956b; Tay and Seah 1975; Tseng et al. 1968; Zaldivar 1977), and similar effects have also been noted only rarely in workers exposed to inorganic arsenic primarily by the inhalation route (Perry et al. 1948). A small fraction of the hyperkeratinized corns may ultimately progress to squamous cell carcinoma of the skin (see below).

Since these skin lesions appear to be the earliest observable sign of chronic exposure, this end point is considered to be the most appropriate for derivation of a chronic-duration MRL. Oral exposure data from studies in humans (Cebrian et al. 1983; Hindmarsh et al. 1977; Southwick et al. 1981; Tseng 1977; Tseng et al. 1968) identify a chronic average daily intake of about 0.01–0.02 mg As/kg/day as the approximate LOAEL for skin lesions, and indicate the NOAEL is between 0.0004 and 0.0009 mg As/kg/day. The NOAEL of 0.0008 mg As/kg/day identified by Tseng et al. (1968) and Tseng (1977) has been selected as the most appropriate basis for calculation of a chronic oral MRL for inorganic arsenic because of the large number of people in the study. However, because the population in the no-effect group were relatively young (only 38% older than 20 and 17% older than 40), there is some chance that dermal effects might not have had time to occur and might become manifest as the population ages. For this reason, the MRL is derived from the NOAEL by an uncertainty factor of three. Chronic inhalation data suggest that exposure of workers to about 0.1–1.0 mg As/m^3 may lead to hyperkeratinization and hyperpigmentation

(Perry et al. 1948), but in the absence of other studies to support this, and without identification of a reliable NOAEL, these data are not considered sufficient for derivation of a chronic inhalation MRL.

Direct dermal contact with inorganic arsenicals may cause irritation and contact dermatitis. Usually the effects are mild (erythema and swelling) but may progress to papules, vesicles, or necrotic lesions in extreme cases (Holmqvist 1951). These conditions tend to heal without treatment if exposure ceases. Effects of this sort have only been observed in workplace environments where there are high levels of arsenic dusts (Holmqvist 1951; Pinto and McGill 1953), and have not been noted in people exposed to arsenic in water or soil (presumably because the concentrations of arsenic that contact the skin from water or soil are too low to cause significant irritation).

Little information was located on dermal effects of organic arsenicals. Workers exposed to arsanilic acid did not complain of dermal problems (Watrous and McCaughey 1945), but no direct examination or comparison of dermal appearance of the workers with a control group was performed. Rats exposed to very high concentrations of DMA developed erythema on the ears and feet along with encrustations around the eyes (Stevens et al. 1979). These effects were presumably due to direct irritation from dermal contact, suggesting that at least some of the organic arsenicals may be able to cause contact dermatitis. However, these data are too limited to draw firm conclusions.

Ocular Effects. Chemical conjunctivitis, characterized by redness, swelling, and pain, usually in combination with facial dermatitis, has been observed in workers exposed to arsenic dusts in air (Dunlap 1921; Pinto and McGill 1953). Facial edema, generally involving the eyelids, was a prominent feature of inorganic arsenic poisoning among 220 cases associated with an episode of arsenic contamination of soy sauce in Japan (Mizuta et al. 1956) and has also been reported in poisoning cases in the United States (Armstrong et al. 1984). The edema developed soon after the initial exposure and then subsided. This effect forms the basis (in part) for the provisional acute oral MRL of 0.005 mg/kg/day for inorganic arsenic.

Little information was located on ocular effects of organic arsenicals.

Immunological and Lymphoreticular Effects. No studies were located on immune and lymphoreticular effects in humans after oral exposure to inorganic arsenicals, but workers exposed to arsenic dusts in air did not have altered levels of antibodies in their blood (Bencko et al. 1988). Mice exposed to arsenate in drinking water did not display any signs of immunotoxicity (Kerkvliet et al. 1980),

and mice given intratracheal doses of sodium arsenite had decreased humoral responsiveness to antigens but no measurable decrease in resistance to bacterial or cellular pathogens (Sikorski et al. 1989). However, mice exposed to arsenic trioxide aerosol for 3 hours had a concentration-related decrease in pulmonary bactericidal activity (presumably as a result of injury to alveolar macrophages) and a corresponding concentration-related increase in susceptibility to introduced respiratory bacterial pathogens (Aranyi et al. 1985). Reports that gallium arsenide suppresses immune function and increases the co-stimulatory activity of macrophages in rodents treated orally or by intraperitoneal injection (Caffrey-Nolan and McCoy 1998; Flora et al. 1998; Lewis et al. 1998a, 1998b) are confounded by the use of gallium nitrate as an immuno-suppressing drug (Makkonen et al. 1995; Orosz et al. 1997). Repeated dermal contact with arsenic dusts in the workplace may lead to dermal sensitization (Holmqvist 1951), but sensitization appears to be very rare in the general population (Wahlberg and Boman 1986). Overall, these data suggest that the immune and lymphoreticular systems are probably not a major target of arsenic, but the data are too sparse to draw firm conclusions.

No studies were located regarding immunological and lymphoreticular effects in humans or animals after exposure to organic arsenicals.

Neurological Effects. Signs of peripheral and/or central neuropathy are common in humans exposed to inorganic arsenicals by the oral route and have also been observed in some workers exposed by the inhalation route. Acute, high-dose exposure can lead to encephalopathy, with clinical signs such as confusion, hallucinations, impaired memory, and emotional lability (Beckett et al. 1986; Danan et al. 1984; Morton and Caron 1989). In fatal or near-fatal cases, this may progress to seizures and coma (Armstrong et al. 1984; Fincher and Koerker 1987), while lower-level exposure can lead to significant peripheral neuropathy (e.g., Feldman et al. 1979; Huang et al. 1985; Landau et al. 1977; Mizuta et al. 1956; Silver and Wainman 1952). This neuropathy is usually first detected as a numbness in the hands and feet, but may progress to a painful "pins and needles" sensation (Franzblau and Lilis 1989; Jenkins 1966; Le Quesne and McLeod 1977). Both sensory and motor neurons are affected, with distal axon degeneration and demyelination (Goebel et al. 1990; Hindmarsh and McCurdy 1986). More advanced symptoms include weakness, loss of reflexes, and wrist-drop or ankle-drop (Chhuttani et al. 1967; Heyman et al. 1956). These effects may diminish after exposure ceases, but recovery is slow and usually is not complete (Beckett et al. 1986; Fincher and Koerker 1987; Le Quesne and McLeod 1977; Morton and Caron 1989; Murphy et al. 1981).

No studies were located regarding neurological effects in humans after exposure to organic arsenicals, but pigs given repeated oral doses of roxarsone developed muscle tremor, paralysis, and seizures (Edmonds and Baker 1986; Rice et al. 1985), along with a degeneration of myelinated axons in the spinal cord (Kennedy et al. 1986). These findings indicate that neurotoxicity may be an effect of concern for organic as well as inorganic arsenicals, but it is not possible to estimate human NOAEL or LOAEL values from the existing data.

Reproductive Effects. Limited information exists on the reproductive effects of inorganic arsenic. Only one human study was located (Lugo et al. 1969), in which a 30-week gestation live infant was delivered after maternal ingestion of 0.39 mg/kg As, and died 11 days later. In addition, few studies have been performed in animals. Reproductive performance was not affected in female rats that received inhalation exposures to concentrations as high as 20 mg As/m^3 or gavage doses as high as 8 mg As/kg/day from 14 days prior to mating through gestation day 19 (Holson et al. 1999, 2000). Schroeder and Mitchner (1971) found a significant increase in the incidence of small litters and a trend toward decreased number of pups per litter in all generations of a 3-generation drinking water study in mice. This finding is consistent with embryolethality produced by inorganic arsenic in developmental toxicity studies (see Developmental Effects, below) and may be due to a lethal effect on the developing organism rather than an effect on the reproductive organs of the parental animals.

Data are also very limited on the reproductive effects of organic arsenicals. No studies were located on effects in humans, but oral exposure of male mice to MMA resulted in a clear decrease in the number of females producing litters (Prukop and Savage 1986). This suggests that MMA might interfere with sperm production, but the effects could also be due to reduced mating as a consequence of illness from nonreproductive effects. Thus, in the absence of additional information, the reproductive toxicity of organic arsenicals cannot be evaluated.

Developmental Effects. There are several epidemiological studies that have reported an association between exposure to inorganic arsenic and increased risk of adverse developmental effects (congenital malformations, low birth weight, spontaneous abortion), both by the inhalation route (Nordstrom et al. 1978a, 1978b, 1979a, 1979b) and the oral route (Aschengrau et al. 1989; Zierler et al. 1988). However, in all of these studies, the populations were exposed to a number of other chemicals and risk factors, which may have contributed to the observed effects, and these studies provide only suggestive evidence that arsenic was a causative agent. Additional suggestive evidence comes from the case of a premature neonate that was born at 30 weeks gestation after maternal ingestion of 0.39 mg As/kg, and died 11 days

later (Lugo et al. 1969). Although most of the findings in the neonate were attributable to immaturity, one remarkable finding at autopsy was severe pulmonary hemorrhage, which the authors suggested may have been due to arsenic. Studies in animals support the view that arsenic is a developmental toxicant, causing reduced birth weight, a variety of fetal malformations (both skeletal and soft tissue), and increased fetal mortality. These effects have been noted following inhalation exposure of mice and rats (Holson et al. 1999; Nagymajtenyi et al. 1985), oral exposure of mice, rats, hamsters, and rabbits (Baxley et al. 1981; Holson et al. 2000; Hood and Harrison 1982; Hood et al. 1978; Nemec et al. 1998; Stump et al. 1999), and intraperitoneal or intravenous injection of rats, mice, and hamsters (Beaudoin 1974; Carpenter 1987; Ferm and Carpenter 1968; Ferm et al. 1971; Hanlon and Ferm 1986c; Hood 1998; Hood and Bishop 1972; Mason et al. 1989; Willhite 1981). However, in all cases, the doses required to cause these effects resulted in significant maternal toxicity or even lethality. Recent studies in mice, rats, and rabbits found no evidence of developmental effects at exposure levels that did not produce maternal toxicity (Holson et al. 1999, 2000; Nemec et al. 1998; Stump et al. 1999). These data suggest that although inorganic arsenic is a developmental toxicant, the developing fetus is not especially susceptible, and teratogenicity or fetotoxicity are unlikely to be of concern except at doses that are also toxic to the pregnant female.

In vitro studies of inorganic arsenic have shown that arsenic is embryotoxic and teratogenic. Arsenic significantly impairs preimplantation mouse blastocyst development at concentrations of 1.1 mg/L, and decreased final cell number in preimplantation embryos in culture at 0.0075 mg/L (Hanna et al. 1997). Studies using mouse whole embryo culture indicate that arsenic causes nonclosure of the cranial neural tube, disruption of optic and otic development, and forebrain growth disruption, which is dependent on gestational age (Tabacova et al. 1996). In addition, postimplantation mouse embryos exposed *in vivo* and then grown *in vitro* exhibited altered neural tube cell cycles (Wlodarczyk et al. 1996).

No studies were located regarding developmental effects in humans after exposure to organic arsenicals. Oral exposure of mice and rats to DMA during gestation resulted in minor fetal effects (malformed palates, decreased weight gain, delayed ossification), although doses that were maternally toxic also caused increased fetal death (Rogers et al. 1981). Intraperitoneal injection of hamsters with MMA or DMA caused no obvious teratogenic or fetotoxic effects at a dose of 54 mg As/kg (Willhite 1981), although very high doses (420–460 mg As/kg/day) caused stunted growth, malformations, and both fetal and maternal deaths (Hood et al. 1982). These studies suggest that the organic arsenicals are significantly less fetotoxic than the inorganic arsenicals, and are not likely to cause developmental effects in humans except at very high exposure levels.

Genotoxic Effects. There have been a large number of studies of the genotoxic effects of arsenic. Tables 2-13 and 2-14 summarize a number of reports on the *in vivo* and *in vitro* genotoxicity of inorganic arsenicals, respectively. The results are mixed, but in general, it appears that the inorganic arsenicals are either inactive or weak mutagens (Jacobson-Kram and Montalbano 1985), but are able to produce chromosomal effects (aberrations, sister chromatid exchange) in most systems. Studies of humans have detected higher-than-average incidence of chromosomal aberrations in peripheral lymphocytes, both after inhalation exposure (Beckman et al. 1977; Nordenson et al. 1978) and oral exposure (Burgdorf et al. 1977; Nordenson et al. 1979). These studies must be interpreted with caution, since in most cases there were only a small number of subjects and a number of other chemical exposures were possible (EPA 1984a). However, the *in vivo* findings are strongly supported by *in vitro* studies using eukaryotic cells (e.g., Lee et al. 1985; Nakamuro and Sayato 1981; Zanzoni and Jung 1980) (see Table 2-14).

The genotoxicity of the organic arsenicals has not been as thoroughly studied, but several tests indicate that DMA and roxarsone may be able to cause mitotic arrest, chromosome aberrations, mutations, and DNA strand breaks (see Table 2-15).

Cancer. There is clear evidence from studies in humans that exposure to inorganic arsenic may increase the risk of cancer. In workers exposed by the inhalation route, the predominant carcinogenic effect is increased risk of lung cancer (e.g., Enterline et al. 1987a, 1987b; Jarup and Pershagen 1991; Jarup et al. 1989; Lee-Feldstein 1986; Welch et al. 1982), although a few reports have noted increased incidence of tumors at other sites (e.g., Lee-Feldstein 1983; Pinto et al. 1977; Tsuda et al. 1987). Based on the risk of lung cancer, EPA has assigned inorganic arsenic to Group A (known human carcinogen) by the inhalation route (IRIS 2000). This is supported by the U.S. Public Health Service, which has also classified inorganic arsenic as a known human carcinogen (NTP 1994, 2000). In general, most researchers observe that risk increases as a function of exposure level and duration (Axelson et al. 1978; Jarup et al. 1989; Lee-Feldstein 1983; Mabuchi et al. 1979; Pinto et al. 1978). Most cases are seen in workers with chronic exposures, although several studies suggest that even short (1 year) exposures may also increase risk (Lee-Feldstein 1986; Sobel et al. 1988). Computer modeling of available epidemiological data suggests that arsenic acts mainly as a promoter, increasing lung cancer by increasing the rate of a late stage in the carcinogenic sequence, although it may also act at an early stage (Brown and Chu 1983c; Enterline and Marsh 1982; Mazumdar et al. 1989).

When exposure occurs by the oral route, the main carcinogenic effect is increased risk of skin cancer. This conclusion is based on a number of epidemiological studies of populations exposed to elevated

Table 2-13. Genotoxicity of Inorganic Arsenic *In Vivo*

Valence	Exposure route	Species (test system)	End point	Results	Reference
Non-mammalian					
As^{+3} As^{+5}	Injection	*Drosophila melanogaster*	Somatic mutations and mitotic recombination	+	Ramos-Morales and Rodriguez-Arnaiz 1995
As^{+3} As^{+5}	Larval feeding	*D. melanogaster*	Somatic mutations and mitotic recombination	+	Ramos-Morales and Rodriguez-Arnaiz 1995
As^{+5}	Larvae	*D. melanogaster*	Mitotic recombinations	+	de la Rosa et al. 1994
Mammalian					
As^{+3}	Inhalation	Human (lymphocytes)	Chromosomal aberrations	–	Beckman et al. 1977
As^{+3}	Inhalation	Human (lymphocytes)	Chromosomal aberrations	+	Nordenson et al. 1978
As^{+3}	Oral	Human (lymphocytes)	Chromosomal aberrations	–	Burgdorf et al. 1977
No data	Oral	Human (lymphocytes)	Chromosomal aberrations	–	Vig et al. 1984
As^{+3}	Oral	Human (lymphocytes)	Sister chromatid exchange	–	Burgdorf et al. 1977
As^{+3}	Oral	Human (lymphocytes)	Sister chromatid exchange	+	Hsu et al. 1997
No data	Oral	Human (lymphocytes)	Sister chromatid exchange	+	Lerda 1994
As^{+3}	Oral	Human (lymphocytes)	Sister chromatid exchange	–	Nordenson et al. 1978
No data	Oral	Human (lymphocytes)	Sister chromatid exchange	–	Vig et al. 1984
No data	Oral	Human skin carcinoma	Mutation and overexpression of p53	+	Hsu et al. 1999
As^{+3}	Oral	Exfoliated human epithelial cells	Micronuclei	+	Moore et al. 1996
No data	Oral	Human (bladder cells)	Micronuclei	+	Moore et al. 1995
As^{+3}	Oral	Human (lymphocytes)	Sister chromatid exchange	+	Hsu et al. 1997
No data	Oral	Human (lymphocytes)	Sister chromatid exchange	+	Lerda 1994
As^{+5}	Oral	Rat (bone marrow cells)	Chromosomal aberrations	+	Datta et al. 1986
As^{+3}	Inhalation	Mouse (fetal liver)	Chromosomal aberrations	(+)	Nagymajtenyi et al. 1985
As^{+3}	Oral	Mouse (bone marrow cells)	Chromosomal aberrations	+	Das et al. 1993

Table 2-13. Genotoxicity of Inorganic Arsenic *In Vivo (continued)*

Valence	Exposure route	Species (test system)	End point	Results	Reference
As^{+3}	Oral	Mouse (bone marrow cells)	Chromosomal breaks, exchanges	–	Poma et al. 1981
As^{+3}	Oral	Mouse (spermatongonia)	Chromosomal aberrations	–	Poma et al. 1981
As^{+3}	Intraperitoneal	Mouse (bone marrow cells)	Chromosomal breaks, exchanges	–	Poma et al. 1981
As^{+3}	Intraperitoneal	Mouse (bone marrow cells)	Micronuclei	+	DeKnudt et al. 1986
As^{+3}	Intraperitoneal	Mouse (spermatogonia)	Spermatongonia	–	Poma et al. 1981
As^{+3}	Intraperitoneal	Mouse (spermatogonia)	Sperm morphology	–	DeKnudt et al. 1986
As^{+3}	Intraperitoneal	Mouse (spermatogenesis)	Dominant lethal mutations	–	DeKnudt et al. 1986

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

Table 2-14. Genotoxicity of Inorganic Arsenic *In Vitro*

Valence	Species (test system)	End point	Results: With activation	Results: Without activation	Reference
	Prokaryotic organisms:				
As^{+3}	*Escherichia coli*	Reveres mutation	No data	+	Nishioka 1975
As^{+3}	*E. coli* PQ37	Gene mutation	No data	–	Lantzsch and Gebel 1997
As^{+3}	*E. coli* (6 strains)	Reverse mutation	No data	–	Rossman et al. 1980
As^{+3}	*Salmonella typhimurium*	Gene mutation	No data	–	Lofroth and Ames 1978
As^{+3}	*Photobacterium fischeri*	Gene mutation	No data	–	Ulitzur and Barak 1988
As^{+5}	*S. typhimurium*	Gene mutation	No data	–	Lofroth and Ames 1978
As^{+5}	*P. fischeri*	Gene mutation	No data	+	Ulitzur and Barak 1988
	Eukaryotic organisms:				
	Fungi:				
As^{+3} As^{+5}	*Saccharomyces cerevisiae*	Gene mutation	No data	–	Singh 1983
	Mammalian cells:				
As^{+3}	Human fibroblasts	DNA repair inhibition	No data	+	Okui and Fujiwara 1986
As^{+3}	Human fibroblasts	DNA repair and mutant frequencies	+	+	Wiencke et al. 1997
As^{+3}	Human fibroblasts	DNA repair inhibition	+	+	Hartwig et al. 1997
As^{+3}	Human fibroblasts (MRC5CV1)	DNA migration	No data	+	Hartmann and Speit 1996
As^{+3}	Human fibroblasts (HFW cells)	Cytotoxicity	No data	+	Lee and Ho 1994
As^{+3}	Human skin fibroblasts (HFW)	Chromosome endoreduplication	No data	+	Huang et al. 1995
As^{+3}	Human skin fibroblasts	Chromosomal aberrations	No data	+	Yih et al. 1997

Table 2-14. Genotoxicity of Inorganic Arsenic *In Vitro (continued)*

Valence	Species (test system)	End point	Results: With activation	Results: Without activation	Reference
	Mammalian cells (continued):				
As^{+3}	Human fetal lung fibroblasts	DNA strand breaks	No data	+	Dong and Luo 1993
As^{+3}	Human fetal lung fibroblasts (2BS cells)	DNA damage and repair	No data	+	Dong and Luo 1994
As^{+3} As^{+5}	Human umbilical cord fibroblasts	Chromosomal aberrations	No data	+	Oya-Ohta et al. 1996
As^{+3}	Diploid human fibroblasts	Morphological transformation	No data	+	Landolph 1994
As^{+3}	Human leukocytes	Chromosomal aberration	No data	+	Nakamuro and Sayato 1981
As^{+3}	Human lymphocytes	DNA protein cross-links	–	–	Costa et al. 1997
As^{+3} As^{+5}	Human lymphocytes	Enhancement or inhibition on DNA synthesis	No data	+	Meng 1993a
As^{+3} As^{+5}	Human lymphocytes	Enhancement or inhibition on DNA synthesis	No data	+	Meng 1993b
As^{+3} As^{+5}	Human lymphocyte	Enhancement or inhibition on DNA synthesis	No data	+	Meng 1994
As^{+3}	Human lymphocytes	Hyperdiploidy and chromosomal breakage	No data	(+)	Rupa et al. 1997
As^{+3}	Human lymphocytes	Hyperdiploid nuclei	No data	+	Ramirez et al. 1997
As^{+3}	Human lymphocytes	Chromosomal aberration	No data	+	Beckman and Nordenson 1986
As^{+3}	Human lymphocyte	Chromosomal aberrations and sister chromatid exchange	No data	+	Nordenson et al. 1981
As^{+3}	Human lymphocytes	Chromosomal aberration	No data	+	Sweins 1983
As^{+3}	Human lymphocytes	Chromosomal aberrations	No data	+	Yager and Wiencke 1993
As^{+3}	Human lymphocytes	Chromosomal aberrations	No data	+	Vega et al. 1995
As^{+3}	Human lymphocytes	Chromosomal aberrations	No data	+	Wan et al. 1982

Table 2-14. Genotoxicity of Inorganic Arsenic *In Vitro (continued)*

Valence	Species (test system)	End point	Results: With activation	Results: Without activation	Reference
	Mammalian cells (continued):				
As^{+3}	Human lymphocytes	Chromosomal aberrations and sister chromatic exchange	No data	+	Wiencke and Yager 1992
As^{+3}	Human lymphocyte	Chromosome aberrations and sister chromatid exchanges	No data	+	Larramendy et al. 1981
As^{+3} As^{+5}	Human lymphocytes	Sister chromatid exchange	No data	+	Gebel et al. 1997
	Human lymphocytes	Sister chromatid exchange	No data	–	
As^{+3}	Human lymphocytes	Sister chromatid exchange	No data	+	Hartmann and Speit 1994
As^{+3}	Human lymphocytes	Sister chromatid exchange	No data	+	Jha et al. 1992
As^{+3}	Human lymphocytes	Sister chromatid exchange	No data	+	Rasmussen and Menzel 1997
As^{+3} As^{+5}	Human T-cell lymphoma-derived cell line (Molt-3)	PARP activity inhibition	No data	+	Yager and Wiencke 1997
As^{+3}	Human cervix carcinoma HeLa and cisplatin-resistant HeLa/CPR variant cells	DNA repair modification	+	+	Chao 1996
As^{+3}	Human cervix carcinoma cells (HeLa)	DNA damage recognition	No data	-	Hartwig et al. 1998
As^{+3}	Human osteosarcoma cells (HOS)	DNA repair	No data	+	Hu et al. 1998
As^{+3}	Mouse lymphoma cells	Enhanced viral forward mutation		(+)	Oberly et al. 1982
As^{+3} As^{+5}	Mouse lymphoma cells (L5178Y/$TK^{+/-}$ -3.7.2C)	Chromosomal mutations	No data	+	Moore et al. 1997a
As^{+3}	Mouse lymphoma cells [L5178Y $tk^{+/-}$ (3.7.sc)]	Mutagenicity	No data	+	Oberly et al. 1996
As^{+3} As^{+5}	Mouse lymphoma cells	Chromosomal aberrations	No data	+	Moore et al. 1994

Table 2-14. Genotoxicity of Inorganic Arsenic *In Vitro (continued)*

Valence	Species (test system)	End point	Results: With activation	Results: Without activation	Reference
As^{+3}	Mouse lymphoma cells	Chromosomal aberrations	No data	+	Sofuni et al. 1996
	Mammalian cells (continued):				
As^{+3}	Mouse 3T6 cells	Gene amplification	No data	+	Lee et al. 1988
As^{+3}	Mouse embryo fibroblasts (C3H/10T/2 Cl8)	Morphological transformation	No data	+	Landolph 1994
As^{+3}	Chinese hamster V79 cells	Gene mutation	No data	–	Li and Rossman 1991
As^{+3}	Chinese hamster V79 cells	Gene mutation	No data	–	Rossman et al. 1980
As^{+3}	Chinese hamster V79 cells	DNA damage, DNA-protein cross-linking, micronucleus induction	No data	+	Gebel et al. 1998a
As^{+3}	Chinese hamster V79 cells	DNA repair and mutant frequencies	No data	+	Li and Rossman 1991
As^{+3}	Chinese hamster ovary cells ($CHO\text{-}A_L$)	Gene mutation	No data	+	Hei et al. 1998
As^{+3}	Chinese hamster ovary cells ($CHO\text{-}AS_{52}$)	Mutagenicity	No data	+	Meng and Hsie 1996
As^{+3}	Chinese hamster ovary cells	Gene mutation	No data	+	Yang et al. 1992
As^{+3}	Chinese hamster ovary cells	DNA repair inhibition	No data	+	Lee-Chen et al. 1993
As^{+3}	Chinese hamster ovary cells	DNA repair inhibition	No data	–	Lee-Chen et al. 1992
As^{+3}	Chinese hamster ovary cells (CHO-K1)	DNA strand breaks	+	+	Lee-Chen et al. 1994
As^{+3}	Chinese hamster ovary cells (CHO-K1)	DNA strand breaks	No data	+	Lynn et al. 1997
As^{+3}	Chinese hamster ovary cells	Aberrant metaphases	No data	+	Jan et al. 1986
As^{+3}	Chinese hamster ovary cells	Aberrant metaphases	No data	+	Lee et al. 1986b

Table 2-14. Genotoxicity of Inorganic Arsenic *In Vitro (continued)*

Valence	Species (test system)	End point	Results: With activation	Results: Without activation	Reference
As^{+3}	Chinese hamster ovary cells	Chromosomal aberrations	+	+	Huang et al. 1992
As^{+3}	Chinese hamster ovary cells (CHO-K1)	Chromosomal aberrations	No data	+	Huang et al. 1993
	Mammalian cells (continued):				
As^{+3} As^{+5}	Chinese hamster ovary cells (CHO-K1)	Chromosomal aberrations and sister chromatid exchange	No data	+	Kochhar et al. 1996
As^{+3}	Chinese hamster ovary cells	Chromosomal aberrations and sister chromatid exchange	+	+	Lin and Tseng 1992
As^{+3}	Chinese hamster ovary cells	Chromosomal aberrations and sister chromatid exchange	No data	+	Wan et al. 1982
As^{+3}	Chinese hamster ovary cells	Sister chromatid exchange and micronucleus induction	No data	+	Fan et al. 1996
As^{+3}	Chinese hamster ovary cells	Cell-killing and micronucleus induction	No data	+	Wang and Huang 1994
As^{+3}	Chinese hamster ovary cells	Micronuclei	No data	+	Liu and Huang 1997
As^{+3}	Chinese hamster ovary cells	Micronuclei formation	No data	+	Yee-Chien and Haimei 1996
As^{+3}	Chinese hamster ovary cells	Micronuclei induction	No data	+	Wang et al. 1997a
As^{+3}	Chinese hamster ovary cells	Cytotoxicity	No data	–	Lee and Ho 1994
As^{+3}	Syrian hamster embryo cells	Gene mutation	No data	–	Lee et al. 1985
As^{+3}	Syrian hamster embryo cells	Chromosome aberrations and sister chromatid exchanges	No data	+	Larramendy et al. 1981

Table 2-14. Genotoxicity of Inorganic Arsenic *In Vitro (continued)*

Valence	Species (test system)	End point	Results: With activation	Results: Without activation	Reference
As^{+3}	Syrian hamster embryo cells	Chromosomal aberration	No data	+	Lee et al. 1985
As^{+3}	Syrian hamster embryo cells	Sister chromatid exchange	No data	+	Lee et al. 1985
As^{+3}	Syrian hamster embryo (SHE) cells	Micronuclei induction	No data	–	Gibson et al. 1997
As^{+3}	Syrian hamster embryo (SHE) cells	Micronuclei induction	No data	–	Gibson et al. 1997
As^{+3}	Syrian hamster embryo cells	Morphological transformation	No data	+	Kerckaert et al. 1996
As^{+3}	Syrian hamster embryo cells	Morphological transformation	No data	+	Lee et al. 1985
As^{+3}	Syrian hamster embryo cells	Morphological transformation	No data	+	Casto et al. 1979
	Mammalian cells (continued):				
As^{+5}	Human fibroblasts	DNA repair inhibition	No data	–	Okui and Fujiwara 1986
As^{+5}	Human leukocyte	Chromosomal aberrations	No data	(+)	Nakamuro and Sayato 1981
As^{+5}	Human lymphocyte	Chromosomal aberrations	No data	–	Nordenson et al. 1981
As^{+5}	Human lymphocyte	Chromosome aberrations and sister chromatid exchanges	No data	+	Larramendy et al. 1981
As^{+5}	Human lymphocytes	Sister chromatid exchange	No data	–	Rasmussen and Menzel 1997
As^{+5}	Human peripheral lymphocytes	Sister chromatid exchange	No data	+	Zanzoni and Jung 1980
As^{+5}	Human keratinocyte line SCC-9 cells	Keratinocyte programming and transcriptional activity	No data	+	Kachinskas et al. 1997
As^{+5}	Mouse lymphoma cells	Gene mutation	No data	–	Amacher and Paillet 1980
As^{+5}	Mouse lymphoma cells	Gene mutation	No data	–	Amacher and Paillet 1980

Table 2-14. Genotoxicity of Inorganic Arsenic *In Vitro (continued)*

Valence	Species (test system)	End point	Results		Reference
			With activation	Without activation	
As^{+5}	Chinese hamster ovary cells	Chromosomal aberrations	No data	+	Wan et al. 1982
As^{+5}	Syrian hamster embryo cells	Gene mutation	No data	–	Lee et al. 1985
As^{+5}	Syrian hamster embryo cells	Chromosome aberrations and sister chromatid exchanges	No data	+	Larramendy et al. 1981
As^{+5}	Syrian hamster embryo cells	Chromosomal aberrations	No data	+	Lee et al. 1985
As^{+5}	Syrian hamster embryo cells	Sister chromatid exchange	No data	+	Lee et al. 1985
As^{+5}	Syrian hamster embryo cells	Morphological transformation	No data	+	Lee et al. 1985
As^{+5}	Syrian hamster embryo cells	Morphological transformation	No data	+	DiPaolo and Casto 1979

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

Table 2-15. Genotoxicity of Organic Arsenic

Chemical form	Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Prokaryotic organisms (*in vitro*):					
Dimethylarsenic acid	*Escherichia coli*	Gene mutation	No data	%	Yamanaka et al. 1989b
Roxarsone	*Salmonella typhimurium*	Gene mutation	–	–	NTP 1989b
Eukaryotic organisms (*in vitro*):					
Arsenobetaine	Human umbilical cord fibroblasts	Chromosomal aberrations	No data	+	Oya-Ohta et al. 1996
Arsenobetaine	Chinese hamster V79 cells	Tetraploids and mitotic arrest	No data	–	Eguchi et al. 1997
Dimethylarsenic acid	Human peripheral lymphocytes	Mitogenesis inhibited	No data	–	Endo et al. 1992
Dimethylarsenic acid	Human lymphocytes	Sister chromatid exchange	No data	–	Rasmussen and Menzel 1997
Dimethylarsenic acid	Human alveolar (L-132) cells	Lung-specific DNA damage	No data	+	Kata et al. 1993
Dimethylarsenic acid	Human alveolar type II (L-132) cells	DNA single-strand breaks	+	+	Kawaguchi et al. 1996
Dimethylarsenic acid	Human diploid L-132 epithelial cells	DNA single-strand breaks	No data	+	Rin et al. 1995
Dimethylarsenic acid	Human alveolar type II (L-132) cells	DNA strand breaks	No data	+	Tezuka et al. 1993
Dimethylarsenic acid	Human embryonic cell line of type II alveolar epithelial cells (L-132)	DNA single-strand breaks and DNA-protein crosslinks	No data	+	Yamanaka et al. 1993
Dimethylarsenic acid	Human alveolar epithelial (L-132) cells	DNA single-strand breaks and DNA-protein crosslinks	No data	+	Yamanaka et al. 1995
Dimethylarsenic acid	Human pulmonary epithelial (L-132) cells	DNA single-strand breaks	No data	+	Yamanaka et al. 1997
Dimethylarsenic acid	Human umbilical cord fibroblasts	Chromosomal aberrations	No data	+	Oya-Ohta et al. 1996
Dimethylarsenic acid	Mouse lymphoma cells (L5178Y/TK$^{+/-}$ -3.7.2C)	Chromosomal mutations	No data	+	Moore et al. 1997a
Dimethylarsenic acid	Chinese hamster lung and diploid cells (V79)	Mitotic arrest and tetraploid formation	No data	+	Endo et al. 1992
Dimethylarsenic acid	Chinese hamster V79 cells	Chromosomal aberrations	No data	+	Ueda et al. 1997
Dimethylarsenic acid	Chinese hamster V79 cells	Tetraploids and mitotic arrest	No data	+	Eguchi et al. 1997
Methylarsonic acid	Human umbilical cord fibroblasts	Chromosomal aberrations	No data	+	Oya-Ohta et al. 1996

Table 2-15. Genotoxicity of Organic Arsenic *(continued)*

Chemical form	Species (test system)	End point	Results		Reference
			With activation	Without activation	
Eukaryotic organisms (*in vitro*): (continued)					
Monomethylarsonic acid	Chinese hamster V79 cells	Tetraploids and mitotic arrest	No data	+	Eguchi et al. 1997
Roxarsone	*Drosophila melanogaster*	Sex linked recessive	No data	–	NTP 1989b
Roxarsone	Rat hepatocyte	DNA double-strand breaks	No data	+	Storer et al. 1996
Roxarsone	A31-1-13 clone of BALB/c-3T3 cells	Transformation response and mutagenicity	No data	–	Matthews et al. 1993
Roxarsone	Mouse lymphoma (L5178Y) cells	Trifluorothymidine resistance	No data	%	NTP 1989b
Eukaryotic organisms (*in vivo*):					
Dimethylarsenic acid	Rat (oral exposure)	DNA single-stand breaks in lung	No data	%	Yamanaka and Okada 1994
Dimethylarsenic acid	Mouse (oral exposure)	DNA strand breaks in tissues	No data	%	Yamanaka et al. 1989b
Dimethylarsenic acid	Mouse (oral exposure)	DNA single-stand breaks in lung	No data	+	Yamanaka et al. 1993
Dimethylarsenic acid	Mouse (oral exposure)	DNA single-strand breaks in lung	No data	–	Yamanaka et al. 1989a
Dimethylarsenic acid	Mouse (injection)	Aneuploidy in bone marrow cells	No data	+	Kashiwada et al. 1998

– = negative result; + = positive result

levels of arsenic in drinking water (e.g., Chakraborty and Saha 1987; Haupert et al. 1996; Luchtrath 1983; Tseng 1977; Tseng et al. 1968; Zaldivar 1974), and on numerous case reports of people exposed to Fowler's solution (Bickley and Papa 1989; Piontek et al. 1989; Sommers and McManus 1953). Based on these findings, the EPA has placed inorganic arsenic in Group A (known human carcinogen) for exposure by the oral route. In addition to skin cancer, there are a number of case reports (Kasper et al. 1984; Lander et al. 1975; Regelson et al. 1968; Roth 1957; Sommers and McManus 1953) and epidemiological studies (Chen et al. 1986, 1988b, 1992; Cuzick et al. 1992; Guo et al. 1997; Kurttio et al. 1999; Lewis et al. 1999; Tsuda et al. 1995a) that indicate ingestion of arsenic also increases the risk of internal tumors (mainly of liver, bladder, kidney, and lung).

As discussed previously (see Section 2.2.2.8), EPA has calculated an oral cancer slope factor for inorganic arsenic based on the dose-response data obtained by Tseng et al. (1968) in Taiwan (IRIS 1999). The Tseng et al. (1968) study has considerable strengths for risk assessment, including a very large sample size, excellent case ascertainment (physical examination), inclusion of both males and females, and lifetime exposure duration. Uncertainties in the assessment include poor nutritional status of the exposed populations, their genetic susceptibility, their exposure to inorganic arsenic from nonwater sources, and the applicability of extrapolating data from Taiwanese to the U.S. population because of different background rates of cancer, possibly genetically determined, and differences in diet other than arsenic (e.g., low protein and fat and high carbohydrate) (IRIS 1999).

The biochemical mechanism of arsenic-induced carcinogenicity is not known. As discussed previously, arsenic does not appear to damage DNA by a direct mechanism, but several studies support the concept that arsenic inhibits one or more of the enzymes involved in DNA replication or repair (Li and Rossman 1989; Nordberg and Anderson 1981; Okui and Fujiwara 1986; Rossman 1981). Another possible mechanism of arsenic-induced carcinogenicity is incorporation of arsenate into DNA in place of phosphate (Nordberg and Anderson 1981). This concept is consistent with observations that arsenate must be present during DNA synthesis in order to be effective, and would explain why arsenic is clastogenic (the arsenate-phosphate bond would be weaker than the normal phosphodiester) but does not cause gene mutations (Jacobson-Kram and Montalbano 1985).

Beneficial Effects. There are several studies in animals that suggest that low levels of arsenic in the diet are beneficial or essential. Rats fed a low-arsenic diet (<0.05 ppm of arsenic in food, corresponding to about 0.0025 mg As/kg/day) did not gain weight normally (Schwartz 1977; Uthus et al. 1983), and arsenic deprivation has been noted to decrease the growth of offspring from rats, goats, and minipigs

(Anke et al. 1976, 1978; Uthus et al. 1983). Decreased reproductive success and increased postnatal mortality has also been noted in goats, minipigs, and rats maintained on low-arsenic diets (Anke et al. 1976, 1978; Uthus et al. 1983). No specific biochemical mechanism is known by which arsenic could be exerting a beneficial effect, but Nielsen et al. (1980) and Uthus et al. (1983) have proposed that arsenic plays a role in arginine and/or zinc metabolism.

While these observations suggest that low levels of arsenic may be essential or beneficial to animals, several researchers consider the weight of evidence inadequate to conclude this with certainty (Hindmarsh and McCurdy 1986; Solomons 1984). EPA (1988e) performed a detailed review of the evidence, and concluded that essentiality, although not rigorously established, is plausible. NRC (1999) also reviewed the evidence for arsenic as an essential element and concluded that the available studies did not provide evidence that arsenic is an essential element in humans, although arsenic supplementation at high doses (concentrations of 350–4,500 ng/g in the diet) does appear to stimulate growth in minipigs, chicks, goats, and rats. If arsenic is essential or beneficial to humans the daily requirement for humans probably lies somewhere between 10 and 50 µg/day (0.0001–0.0007 mg As/kg/day) (EPA 1988e; NAS 1977b). This level of arsenic intake is usually provided in a normal diet (about 50 µg/day; see Section 5.5), and no cases of arsenic deficiency in humans have ever been reported.

Arsenic has long been used for medicinal purposes. As Fowler's solution (1% arsenic trioxide), it was used in the 19th and early 20th century to treat a wide variety of ailments, particularly skin diseases, asthma, fevers, and pain (NRC 1999). Organic arsenic antibiotics were used extensively in the early 20th century to treat protozoal and spirochetal diseases, such as syphilis, but these compounds were largely replaced by penicillin in the 1940s and 1950s. Recent studies have described the use of inorganic arsenic to treat acute promyelocytic leukemia. Intravenous injection with 10 mg/day or 0.5 mg/kg/day of arsenic trioxide has been reported to induce remission in patients suffering this disease (Bergstrom et al. 1998; Huang et al. 1998; Shen et al. 1997; Soignet et al. 1998). Arsenic trioxide appears to selectively induce apoptosis in leukemia cells (Akao et al. 1998; Bazarbachi et al. 1999; Chen et al. 1997a; Lu et al. 1999; Rousselot et al. 1999; Zhu et al. 1997). A number of different mechanisms by which arsenic trioxide may trigger apoptosis have been proposed. These include down regulation of Bcl-2 (Akao et al. 1998), direct interaction with tubulin (Li and Broome 1999), degradation of the leukemia specific protein PML/RARα (Zhu et al. 1997), and opening the mitochondrial permeability transition pore allowing the release of an apoptosis-inducing factor (Larochette et al. 1999). It has also been suggested that cells with lower levels of GSH have greater sensitivity to the effects of arsenic trioxide (Dai et al. 1999) and that combining

arsenic trioxide treatment with interferon can produce a synergistic improvement in the effectiveness of therapy.

2.6 ENDOCRINE DISRUPTION

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, or otherwise interfere with the normal function of the endocrine system. Chemicals with this type of activity are most commonly referred to as endocrine disruptors. Some scientists believe that chemicals with the ability to disrupt the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. Others believe that endocrine disrupting chemicals do not pose a significant health risk, particularly in light 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 compounds are derived from plants and are similar in structure and action as endogenous estrogen. While there is some controversy over the public health significance of endocrine disrupting chemicals, it is agreed that the potential exists for these compounds to affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, reproduction, development, and/or behavior (EPA 1997h). As a result, endocrine disruptors may play a role in the disruption of sexual function, immune suppression, and neurobehavioral function. Endocrine disruption is also thought to be involved in the induction of breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

There is little evidence to suggest that arsenic functions as an endocrine disruptor. Rahman et al. (1998) reported a correlation between exposure to arsenic in the drinking water and increased incidence of diabetes mellitus in residents of Bangladesh, but no other relevant data were located in humans or animals.

2.7 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 5.6 Exposures of Children.

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

Arsenic has been recognized as a human toxicant for many centuries, and the symptoms of acute poisoning are well known. Children who are exposed to high levels of arsenic exhibit symptoms similar to those seen in adults, including respiratory, cardiovascular, dermal, and neurological effects, and vomiting if the arsenic is ingested (Borgono et al. 1980; Foy et al. 1992; Kersjes et al. 1987; Rosenberg 1974; Zaldivar 1974; Zaldivar and Gullier 1977). Arterial thickening of the pancreas was observed in five children who died in Chile after chronic exposure to arsenic (Rosenberg 1974). Foy et al. (1992) described systemic effects of chronic arsenic exposure in children in a village near a tin and tungsten mining operation in Thailand. The arsenic concentration in water samples from 35 shallow wells averaged 0.82 mg As/L (range, 0.02–2.7 mg As/L). Piped water (available in some homes) had a concentration of 0.07 mg As/L. A survey of skin manifestations of arsenic poisonings was conducted in the autumn of 1987. The case reports of four children were presented. All of the children had hyperkeratosis and hyperpigmentation (Blackfoot disease) of the extremities, including tibia, palms, and soles. In addition, one child had developed weakness 3 years previously and had anorexia and a chronic cough for 1 year. She had been held back twice in school as a slow learner. On examination, she had a runny nose and weakness of her wrist joints. The liver was about 4 finger-breadths below the right costal margin with a sharp but tender edge. Blood arsenic levels ranged from 0.087 to 0.46 µg/mL and the arsenic level in hair ranged from 14.4 to 20 µg/g. The authors concluded that the finding of typical skin manifestations of chronic arsenic poisoning suggests that it may take a considerably shorter period of time to develop these manifestations than previously thought. However, it is not known what effect co-exposure to tin and tungsten might have had on skin manifestations in these children.

Wulff et al. (1996) conducted a retrospective study of a cohort of children born between 1961 and 1990 in the municipality of Skelleftea, Sweden, where a smelter released arsenic and other pollutants including lead, copper, cadmium, and sulfur dioxide. Childhood cancer incidences among children born in the vicinity of the smelter (i.e., within 20 km) and distant from the smelter (>20 km) were compared with expected incidences based on Swedish national statistics. There appeared to be an increased risk of childhood cancer (all types combined) among children born in the vicinity of the smelter (SIR=195, 95% CI=88–300, based on 13 cases observed and 6.7 expected), but the increase was not statistically significant, and in any event, the role of arsenic in any finding from this study is confounded by the presence of other metals. The number of cases (n=42) was very close to the expected number (n=41.8) among children born distant from the smelter.

Inorganic arsenic has been characterized as a developmental toxicant. It is known to cross the placental barrier and selectively accumulate in the neuroepithelium of the developing animal embryo (Hanlon and Ferm 1977; Lindgren et al. 1984). Studies in animals have also revealed that various fetal malformations occur after embryonic exposure to arsenic *in vitro*; neural tube defects are the predominant and consistent malformation in these studies (Chaineau et al. 1990; Mirkes and Cornel 1992; Morrissey and Mottet 1983; Mottet and Ferm 1983; Tabacova et al. 1996; Willite and Ferm 1984; Wlodarczyk et al. 1996). *In vivo* studies have shown that high doses of ingested arsenic can produce developmental effects (fetal mortality, skeletal defects), but only at maternally toxic doses (Baxley et al. 1981; Holson et al. 1999, 2000; Hood and Harrison 1982; Hood et al. 1978; Nemec et al. 1998; Stump et al. 1999). In humans, acute prenatal exposure to high doses of inorganic arsenic can result in miscarriage and early neonatal death (Bollinger et al. 1992; Lugo et al. 1969). Although several studies have reported marginal associations between prolonged low-dose human arsenic exposure and adverse reproductive outcomes, including spontaneous abortion, stillbirth, developmental impairment, and congenital malformation (Aschengrau et al. 1989; Nordstrom et al. 1978a, 1979b; Zierler et al. 1988), none of these studies have provided convincing evidence for such effects.

There is no evidence for differences in absorption of arsenic in children and adults. Ingestion of arsenic in dirt may be an important route of exposure for young children. A study that used a synthetic gastric juice designed to mimic gastric conditions in a 2-year-old child found that absorption of arsenic from contaminated soil was likely to be up to 5 times lower than the total concentration of arsenic in the soil (Williams et al. 1998). As previously mentioned, arsenic crosses the placenta and preferentially accumulates in the embryonic neuroepithelium. In addition, arsenic is known to be present in breast milk at low concentrations. Arsenic concentrations were low in human milk sampled from 88 mothers in the Faroe Islands (0.0001–0.0044 ppm), where the diet is predominantly seafood (exposures were primarily to "fish arsenic" [Grandjean et al. 1995]), in a population of Andean women (0.0008–0.008 ppm) exposed to high concentrations of inorganic arsenic in drinking water (Concha et al. 1998b), and in a World Health Organization survey (0.00013–0.00082 ppm) (Somogyi and Beck 1993). There is no information in the literature describing storage of arsenic in maternal tissues. There is some evidence that metabolism of arsenic in children is less efficient than in adults. Children in two villages in Argentina ingesting large amounts of arsenic in their drinking water (200 µg/L) excreted about 49% inorganic arsenic and 47% DMA, compared to 32% inorganic arsenic and 66% DMA for the women in the study (Concha et al. 1998b). No PBPK models specifically targeted at fetuses, infants or children, or pregnant or lactating women were found in the literature. There are no biomarkers that have been specifically identified for

children exposed to arsenic. In addition, no unique interactions of arsenic with other chemicals have been identified in children.

The mechanism of action of arsenic in the mammalian cell involves inhibition of proliferation of cells (Dong and Luo 1993; Jha et al. 1992; Petres et al. 1977). In addition, arsenic impairs assembly and disassembly of microtubules, thus interfering with mitotic spindle formation and embryonal cell division (Leonard and Lauwerys 1980; Li and Chou 1992; Mottet and Ferm 1983). Arsenic compounds also cause chromosomal aberrations (Jha et al. 1992; Leonard and Lauwerys 1980), which disrupt cell cycling. The direct toxic effects of arsenic in the developing embryo result not from a difference in the mechanism of toxicity during development, but rather from the existence of a unique target tissue, the neuroepithelium. The process of neurulation involves cell shape changes, cytokinesis, and cell adhesion, which are dependent upon cytoskeletal elements that are functionally affected by arsenic (Dallaire and Beliveau 1992; Edelman 1992; Gunn et al. 1992; Li and Chou 1992; Moriss-Kay et al. 1994; Scheonwolf and Smith 1990; Taubeneck et al. 1994). However, since arsenic is known to affect vasculature, and since altered placental and/or embryonal vasculature has been suggested as a mechanism leading to neural tube defects, the embryo may be especially sensitive to this manifestation of arsenic toxicity.

2.8 BIOMARKERS OF EXPOSURE AND EFFECT

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

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

substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to arsenic are discussed in Section 2.8.1.

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 arsenic are discussed in Section 2.8.2.

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 2.10, "Populations That Are Unusually Susceptible".

2.8.1 Biomarkers Used to Identify or Quantify Exposure to Arsenic

Arsenic levels in blood, urine, hair, and nails have all been investigated and used as biological indicators of exposure to arsenic. Since arsenic is cleared from blood within a few hours (Tam et al. 1979b; Vahter 1983), measurements of blood arsenic reflect exposures only within the very recent past. Typical values in nonexposed individuals are less than 1 µg/L (Heydorn 1970; Hindmarsh and McCurdy 1986; Valentine et al. 1979). Consumption of medicines containing arsenic is associated with blood values of 100–250 µg/L, while blood levels in acutely toxic and fatal cases may be 1,000 µg/L or higher (Driesback 1980).

However, blood levels do not appear to be reliable indicators of chronic exposure to low levels of arsenic. For example, there was no correlation between the level of arsenic in blood of residents and the level of arsenic in drinking water in several U.S. communities where water levels ranged from about 6 to 125 µg/L (Valentine et al. 1979, 1981). Consequently, measurement of blood arsenic is not generally considered to be a reliable means of monitoring human populations for arsenic exposure.

As discussed in Section 2.3.4, most arsenic that is absorbed from the lungs or the gastrointestinal tract is excreted in the urine, mainly within 1–2 days. For this reason, measurement of urinary arsenic levels is generally accepted as the most reliable indicator of recent arsenic exposure, and this approach has proved useful in identifying above-average exposures in populations living near industrial point sources of arsenic (e.g., Milham and Strong 1974; Polissar et al. 1990). By the inhalation route, several researchers have found that there is a good quantitative correlation between the concentration of arsenic in workplace air (C_{air}, $\mu g/m^3$) and the concentration in the urine (C_{urine}, $\mu g/L$) of exposed workers. For example, Pinto et al. (1976) found a linear relationship for exposures ranging up to 150 $\mu g/m^3$, given by the following equation:

$$C_{air}=0.3\ C_{urine}$$

More recently, Enterline et al. (1987a) reinvestigated this relationship over a wider range of exposures (up to 3,500 $\mu g/m^3$), and found that the curve tended to be concave upward, as given by the following equation:

$$C_{air}=0.0064\ (C_{urine})^{1.94}$$

This indicates that at higher exposure levels, a higher fraction of the dose is excreted in urine, although the toxicokinetic basis for this is not certain. Numerous studies have used above-average urinary levels (i.e., higher than about 100 µg/L) as evidence of recent arsenic ingestion (e.g., Borgono et al. 1980; Fincher and Koerker 1987; Franzblau and Lilis 1989; Goldsmith and From 1986; Kyle and Pease 1965; Valentine et al. 1981), but a quantitative relation between ingested arsenic and urinary excretion levels has only recently been reported. Calderon et al. (1999) found a quantitative correlation between the log of the mean total urinary arsenic concentration/creatinine (TAs/c, µg/mg) of people living in areas with arsenic-contaminated drinking water sources and the log of the inorganic arsenic concentration in the drinking water (InAs, µg/L). The equation for the regression line is:

$$TAs/c=10^{-2.57}\ x\ (InAs)^{0.63}$$

where -2.57 and 0.63 are the intercept and slope, respectively, for the regression of the log10-transformed data. Mixed model regression analysis showed that the log of estimated arsenic intake from drinking water (µg/day) is also a good predictor of Tas/c excretion (Calderon et al. 1999).

There is some indication that speciation of urinary arsenic may indicate the extent of past cumulative exposure to arsenic. Hsueh et al. (1998a) reported higher levels of DMA and MMA in the urine of individuals with higher cumulative past exposure to inorganic arsenic. Speciated urinary arsenic is also a recommended biomarker for recent inorganic arsenic exposure. Walker and Griffin (1998) used the EPA Exposure Assessment Model and a number of site-specific data covering environmental and biological factors to predict total and speciated urinary arsenic concentrations for children living near high levels of arsenic-contaminated soil. There was reasonable agreement between the measured and predicted speciated urinary arsenic concentrations.

An important limitation to the use of total urinary arsenic as a biomarker of exposure is that arsenobetaine is excreted (unmetabolized) in urine after ingestion of certain seafoods (Brown et al. 1990; Kalman 1987; Tam et al. 1982). Since "fish arsenic" is essentially nontoxic, analytical methods based on total urinary arsenic content may overestimate exposures to arsenic species that are of health concern. As discussed in Section 6.1, there are adequate methods for distinguishing arsenobetaine from other forms of arsenic in urine (inorganic, MMA, DMA), although these are not convenient to use as a routine screening method.

Arsenic tends to accumulate in hair and nails, and measurement of arsenic levels in these tissues may be a useful indicator of past exposures. Normal levels in hair and nails are 1 ppm or less (Choucair and Ajax 1988; Franzblau and Lilis 1989). These values may increase from several-fold to over 100-fold following arsenic exposure (Agahian et al. 1990; Bencko et al. 1986; de Peyster and Silvers 1995; Karagas et al. 1996; Landau et al. 1977; Milham and Strong 1974; Southwick et al. 1981; Valentine et al. 1979; Yamauchi et al. 1989) and remain elevated for 6–12 months (Choucair and Ajax 1988). Minimum exposure levels that produce measurable increases in arsenic levels in hair and nails have not been precisely defined. For hair, ingestion of 50–120 ppb of arsenic in drinking water produced only a marginal effect, but a clear increase was noted at 393 ppb (Valentine et al. 1979). Inhalation exposure of workers to about 0.6 µg/m^3 of arsenic in air significantly increased average levels in nails (Agahian et al. 1990), although there was wide variation between individuals.

Analysis of hair may yield misleading results due to the presence of arsenic adsorbed to the external surface, but this can be minimized by collecting samples from close to the scalp or from unexposed areas and by washing the hair before analysis (e.g., Paschal et al. 1989). Similarly, extensive washing of nails is required to remove exogenous contamination (Agahian et al. 1990). The relationship between consumption of food items and levels of arsenic in toenails has recently been evaluated by MacIntosh et al. (1997) using standard multivariate regression models. This approach does not appear to be highly

reliable, but may be sufficient for exploring associations between diet and disease. Kurttio et al. (1998) used linear regression models to show that there is a good association between arsenic concentration in hair (mg/kg) and total arsenic concentration in urine (µg/L), arsenic concentration in drinking water (µg/L) or daily intake of arsenic (µg/day). A 10 µg/L increase in the drinking water concentration or a 10–20 µg/day increase in daily arsenic intake corresponded to a 0.1 mg/kg increase in the arsenic concentration in hair.

2.8.2 Biomarkers Used to Characterize Effects Caused by Arsenic

As discussed in Section 2.2, the characteristic pattern of skin changes caused by arsenic (hyperkeratinization, hyperpigmentation) is probably the most sensitive and diagnostic clinical indicator of chronic exposure to arsenic. However, no means has been developed for detecting these effects except by routine dermatological examination.

Peripheral neuropathy is another characteristic effect of arsenic exposure, and several researchers have investigated decreased nerve conduction velocity or amplitude as a biomarker for peripheral neuropathy. While effects can usually be detected in individuals with clinical signs of neuropathy (e.g., Goebel et al. 1990; Jenkins 1966; Le Quesne and McLeod 1977; Morton and Caron 1989; Murphy et al. 1981), effects are only marginal (Hindmarsh et al. 1977; Landau et al. 1977; Valentine et al. 1981) or undetectable (Kreiss et al. 1983; Southwick et al. 1981) in exposed populations without obvious clinical signs of toxicity. This indicates that this approach is probably not sufficiently sensitive to detect neurological effects earlier than by standard neurological examination (Hindmarsh and McCurdy 1986). Also, decreases in nerve conduction velocity or amplitude are not specific for arsenic-induced neuropathy.

Arsenic is known to affect the activity of a number of enzymes, and some of these may have potential as biomarkers of effect. Most promising is the spectrum of effects caused by arsenic on the group of enzymes responsible for heme synthesis and degradation, including inhibition of coproporphyrinogen oxidase and heme synthetase (Woods and Fowler 1978; Woods and Southern 1989) and activation of heme oxygenase (Sardana et al. 1981). Menzel et al. (1998) has examined the *in vitro* induction of human lymphocyte heme oxygenase 1(HO1) as a biomarker of arsenite exposure. Arsenite did induce de novo synthesis of HO1 in human lymphoblastoid cells, but it has not been determined if the same response is induced *in vivo*. It has been shown in animals that these arsenic-induced enzymic changes result in increased urinary levels of uroporphyrin, coproporphyrin, and bilirubin (Albores et al. 1989; Woods and Fowler 1978), and it has been shown that these effects can be detected in the urine of arsenic-exposed

humans (Garcia-Vargas and Hernandez-Zavala 1996). Therefore, altered urinary levels of these heme-related compounds could serve as a biomarker of effect. However, it is known that numerous other toxic metals also have similar effects on heme metabolism (Albores et al. 1989; Sardana et al. 1981; Woods and Southern 1989), so it is likely that these effects would not be specific for arsenic.

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

2.9 INTERACTIONS WITH OTHER CHEMICALS

A number of researchers have found that arsenic compounds tend to reduce the effects of selenium (Hill 1975; Howell and Hill 1978; Kraus and Ganther 1989; Levander 1977; Moxon et al. 1945; Schrauzer 1987; Schrauzer et al. 1978). Likewise, selenium can decrease the effects of arsenic, including clastogenicity (Beckman and Nordenson 1986; Biswas et al. 1999; Sweins 1983), cytotoxicity (Babich et al. 1989; Rossner et al. 1977), and teratogenicity (Holmberg and Ferm 1969). The mechanism of this mutual inhibition of effects is not known, but may be related to the formation of a complex that is excreted more rapidly than either arsenic or selenium alone (Cikrt et al. 1988; Hill 1975; Levander 1977; Levander and Baumann 1966). There is little direct evidence that variations in selenium exposure in humans lead to significant increases or decreases in arsenic toxicity, although copper smelter workers who developed lung cancer had lower tissue levels of selenium than workers who did not develop lung tumors (Gerhardsson et al. 1985, 1988). This suggests that selenium deficiency could significantly increase the risk of lung cancer following inhalation exposure to arsenic, but it is difficult to distinguish cause from effect in such a study.

The interaction between cigarette smoking, inhalation of arsenic, and the risk of lung cancer has not been extensively investigated. Smoking appeared to increase lung cancer risk synergistically (multiplicatively) in one study of smelter workers (Pershagen et al. 1981), although the data are not adequate to exclude a simple additive interaction (Thomas and Whittemore 1988). Suggestive evidence of a positive interaction between arsenic and benzo(a)pyrene has also been noted for induction of lung adenocarcinomas in hamsters (Pershagen et al. 1984a).

Co-exposure to ethanol and arsenic may exacerbate the toxic effects of arsenic. Simultaneous exposure of rats to ethanol (10% in drinking water) and arsenic (dose not stated) for 6 weeks produced a significant

increase in the concentration of arsenic in the kidney, a nonsignificant increase of arsenic in the liver and a significant increase in the concentration of glutathione in the liver, compared to rats treated with either ethanol or arsenic alone (Flora et al. 1997a, 1997b). Histological damage to the liver, but not the kidneys, was increased in rats treated with both ethanol and arsenic compared to those receiving only arsenic.

Studies of rats exposed to arsenic, lead, and cadmium, alone or in combination, have revealed mainly additive or subadditive effects on body weight, hematological parameters, and enzymes of heme synthesis (Mahaffey and Fowler 1977; Mahaffey et al. 1981). Similarly, studies of the tissue levels of arsenic in rats fed arsenic with or without lead or cadmium revealed only limited evidence of any toxicokinetic interactions (Mahaffey et al. 1981). Pretreatment of rats with a nontoxic dose of cadmium had no effect on the lethality of a high dose of arsenic and did not reduce arsenic-induced hepatotoxicity (Hochadel and Waalkes 1997). These data do not suggest that arsenic toxicity is likely to be significantly influenced by concomitant exposure to these metals. However, supplementation with zinc or chromium may be useful in reducing chronic arsenism. Arsenic has been shown to cause an increase in total plasma cholesterol; co-administration of chromium(III) counteracts this effect (Aguilar et al. 1997). Pretreatment of mice with zinc, at least 24 hours before injection with arsenic-73, reduced arsenic retention compared to controls that did not receive the zinc pretreatment or received it only a short time before the administration of arsenic (Kreppel et al. 1994). Zinc is an inducer of metallothionein, but this induction does not appear to be the mechanism that reduces arsenic toxicity because other inducers of metallothionein did not reduce arsenic toxicity and arsenic elimination was increased by the zinc pretreatment.

Since methylation of arsenic is a detoxification mechanism, it is possible that chemicals that interfere with the methylation process could increase toxicity. This is supported by studies in animals in which reagents that inhibit methylation enzymes (e.g., periodate-oxidized adenosine) caused an increase in tissue levels of inorganic arsenic (Marafante and Vahter 1986, Marafante et al. 1985). Similarly, cellular glutathione levels appear to play a role in the methylation process, and treatment with reagents (e.g., phorone) that decrease glutathione levels increases arsenic toxicity (Buchet and Lauwerys 1987). Inadequate dietary intake of methionine, choline, or protein may also exacerbate arsenic toxicity. Rabbits pretreated with diets low in choline, methionine, or protein showed a significant increase in tissue retention of arsenic and a significant decrease in the excretion of dimethylarsinic acid (Vahter and Marfante 1987). The increased retention of arsenic in rabbits fed these deficient diets is likely to be due to a reduction in arsenic methylation. Thus, the toxic effects of chronic arsenic ingestion may be increased in populations that are also subject to malnutrition.

2.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to arsenic than will most persons exposed to the same level of arsenic 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 arsenic, or compromised function of organs affected by arsenic. Populations who are at greater risk due to their unusually high exposure to arsenic are discussed in Section 5.7, Populations With Potentially High Exposures.

No studies were located regarding unusual susceptibility of any human subpopulation to arsenic. However, since the degree of arsenic toxicity may be influenced by the rate and extent of its methylation in the liver (see Section 2.3.3), it seems likely that some members of the population might be especially susceptible because of lower than normal methylating capacity. Reduced hepatic methylation could result from dietary deficiency of methyl donors such as choline or methionine (Buchet and Lauwerys 1987; Vahter and Marafante 1987), although this is unlikely to be a concern for most people in the United States. While there is some evidence that methylation capacity does vary among individuals (e.g., Buchet et al. 1981a; Foa et al. 1984; Tam et al. 1979b), the basis of this variation and its impact on human susceptibility have not been established. One report did describe severe arsenic toxicity, including neuropathy, that developed only in a 5,10-methylenetetrahydrofolate-reductase (MTHFR) deficient member of a family that had been exposed to arsenic (Brouwer et al. 1992). The authors suggest that the MTHFR deficiency in this girl might explain the fact that of all the family members exposed to arsenic, only she developed severe clinical signs of arsenic poisoning. Liver disease does not appear to decrease methylation capacity in humans, at least at low levels of arsenic exposure (Buchet et al. 1982; Geubel et al. 1988).

2.11 METHODS FOR REDUCING TOXIC EFFECTS

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

Tintinalli JE, Ruiz E, Krone RL, eds. 1996. Emergency medicine. A comprehensive study. American College of Emergency Physicians. 4th ed. The McGraw-Hill Companies, Inc.

Goldfrank RL, et al. 1994. Goldfrank's toxicologic emergencies. 5th ed. Appleton and Lange 5th Edition.

Ellenhorn MJ, Barceloux DG. 1988. Medical toxicology: Diagnosis and treatment of human poisoning. New York, NY: Elsevier Science Publishing Company, Inc.

2.11.1 Reducing Peak Absorption Following Exposure

No data were located regarding the reduction of absorption after inhalation exposure to arsenic.

There are a number of methods for reducing absorption of arsenic following oral exposure. In cases of acute high-dose exposure, the removal of arsenic from the gastrointestinal tract may be facilitated by consumption of large volumes of water, gastric lavage, stomach intubation, induced emesis, or use of cathartics (saline, sorbitol) within a few hours after ingestion (Aposhian and Aposhian 1989; ATSDR 1990; Campbell and Alvarez 1989; Driesback 1980; Ellenhorn and Barceloux 1988; EPA 1989e; Haddad and Winchester 1990; Kamijo et al. 1998; Stutz and Janusz 1988). However, the efficacy of several of these methods has been questioned by some authors, and in some cases, the treatments may be contraindicated. For example, vomiting and diarrhea often occur soon after ingesting arsenic, and therefore, use of an emetic or cathartic may not be necessary. Also, emesis should not be induced in obtunded, comatose, or convulsing patients (Campbell and Alvarez 1989; Ellenhorn and Barceloux 1988; EPA 1989e), and saline cathartics should be used with caution in patients with impaired renal function (Campbell and Alvarez 1989). Treatments of this sort are unlikely to be required following low-level exposures.

Another possible approach for reducing absorption following oral exposure is to administer substances that bind the arsenic in the gastrointestinal tract. For example, activated charcoal is sometimes used for this purpose (Campbell and Alvarez 1989; EPA 1989e; Stutz and Janusz 1988), although the effectiveness of this treatment is not well established. Because pentavalent arsenic is a phosphate analogue, administration of phosphate-binding substance such as aluminum hydroxide might possibly be useful, but this has not been investigated. Sulfhydryl compounds might be given to bind trivalent arsenic, but is

seems unlikely that these would be effective under the acid conditions in the stomach, and it is not clear that such complexes would have reduced gastrointestinal absorption.

Following dermal or ocular exposure to arsenic, several measures can be taken to minimize absorption. All contaminated clothing should be removed, and contacted skin should be immediately washed with soap and water. Eyes that have come in contact with arsenic should be flushed with copious amounts of clean water (EPA 1989e; Stutz and Janusz 1988).

2.11.2 Reducing Body Burden

Acute arsenic intoxication may require treatment with chelating agents such as dimercaprol (BAL) and D-penicillamine. Although body burden is not necessarily reduced, these chelators bind free arsenic and serve to reduce the body's pool of biologically active arsenic. Chelation therapy is most effective when instituted within a few hours after exposure, and efficacy decreases as time after exposure increases (ATSDR 1990; Kajimo et al. 1998; McFall et al. 1998; Peterson and Rumack 1977).

In general, chelating agents should be used with caution, since they may have serious side effects such as pain, fever, hypotension, and nephrotoxicity (Ellenhorn and Barceloux 1988). Some water-soluble and less toxic analogues of BAL such as dimercaptosuccinic acid (DMSA), dimercaptopropyl phthalamadic acid (DMPA), and dimercaptopropane sulfonic acid (DMPS) are currently under investigation and may prove to be promising treatments for arsenic poisoning (Aposhian and Aposhian 1989; Aposhian et al. 1997; ATSDR 1990; Guha Mazumder 1996; Kreppel et al. 1995). However, a randomized placebo trial of 2,3-dimercaptosuccinic acid as a therapy for chronic arsenosis due to drinking contaminated water found no significant difference between patients treated with 2,3-dimercaptosuccinic acid and those treated with a placebo (Guha Mazumder et al. 1998b). N-acetylcysteine has been used in animals to chelate arsenic (Haddad and Winchester 1990), and a human case study reported N-acetylcysteine to be successful in treating a case of arsenic poisoning that was not responding well to BAL treatment (Martin et al. 1990).

As discussed in Section 2.3.3, once arsenic has been absorbed into the blood stream, it undergoes methylation to yield MMA and DMA. These forms of arsenic are less toxic than inorganic arsenic and are cleared from the body by excretion in the urine. Therefore, if it were possible to enhance arsenic methylation, both body burden and toxicity of arsenic might be reduced. However, experimental evidence in animals and humans suggests that arsenic methylation is not enhanced to any significant

degree by supplementation with methylation cofactors (Buchet and Lauwerys 1987; Buchet et al. 1982), presumably because it is enzyme level and not cofactor availability that is rate limiting in arsenic methylation.

2.11.3 Interfering with the Mechanism of Action for Toxic Effects

It is generally thought that trivalent arsenic exerts its toxic effects mainly by complexing with sulfhydryl groups in key enzymes within the body, thereby inhibiting critical functions such as gluconeogenesis and DNA repair (Aposhian and Aposhian 1989; Li and Rossman 1989). Therefore, administration of sulfhydryl-containing compounds soon after exposure could provide alternative target molecules for arsenic, and prevent inhibition of enzyme functions. In fact, many of the chelating agents discussed above (BAL, DMSA, DMPA, DMPS, N-acetylcysteine) contain sulfhydryl groups, and this may account for their efficacy.

The mechanism by which pentavalent arsenic acts is less certain. Since pentavalent arsenic is reduced in the body to the trivalent state, pentavalent arsenic may act in a similar manner as described above for trivalent arsenic. If this is the case, efforts to inhibit the reduction of pentavalent arsenic would decrease its toxicity. However, no methods are currently recognized for blocking this reduction. Pentavalent arsenic may also exert effects by acting as a phosphate analogue. As a phosphate analogue, pentavalent arsenic could potentially affect a number of biological processes, including ATP production, bone formation, and DNA synthesis. However, any effort to interfere in normal phosphate metabolism could produce serious side effects, and no method is known for selectively interfering with arsenate metabolism.

2.12 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 arsenic 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 arsenic.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would

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

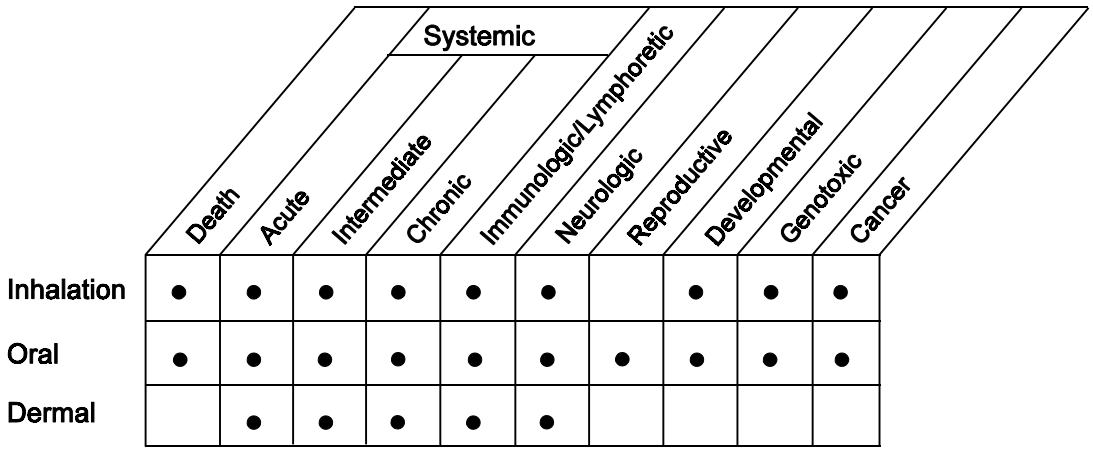
2.12.1 Existing Information on Health Effects of Arsenic

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to arsenic are summarized in Figures 2-9 and 2-10. The purpose of this figure is to illustrate the existing information concerning the health effects of arsenic. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

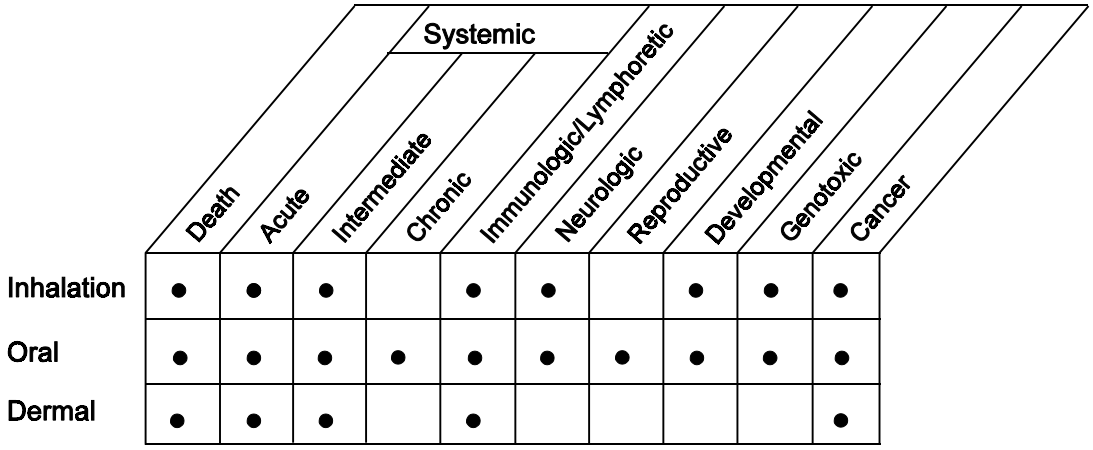
As shown in Figure 2-9, there is a substantial database on the toxicity of inorganic arsenicals, both in humans and in animals. The oral route has been most thoroughly investigated, and reports are available on most end points of concern following acute, intermediate, and chronic exposure. The inhalation route has also been studied extensively, mainly in humans, with special emphasis on lung cancer. A number of noncancer end points have also been studied following inhalation exposure, but information on these effects is less extensive. Limited information on the effects of dermal exposure is also available in both humans and animals, focusing mainly on direct irritancy and dermal sensitization reactions. The absence of studies on other effects of inorganic arsenic following dermal exposure is probably not a critical data need, since dermal uptake of inorganic arsenic appears to be sufficiently limited that other routes of exposure (oral or inhalation) would almost always be expected to be of greater concern.

As shown in Figure 2-10, very little information is available on the effects of organic arsenic compounds in humans, although there are a number of studies in animals. These studies mainly involve the oral route, since all of these compounds are nonvolatile solids, although a few acute inhalation studies have been performed. Limited information is available on acute dermal lethality and dermal irritancy of some organic arsenicals, but data are lacking on other effects of organic arsenicals following dermal exposure.

Figure 2-9. Existing Information on Health Effects of Inorganic Arsenic



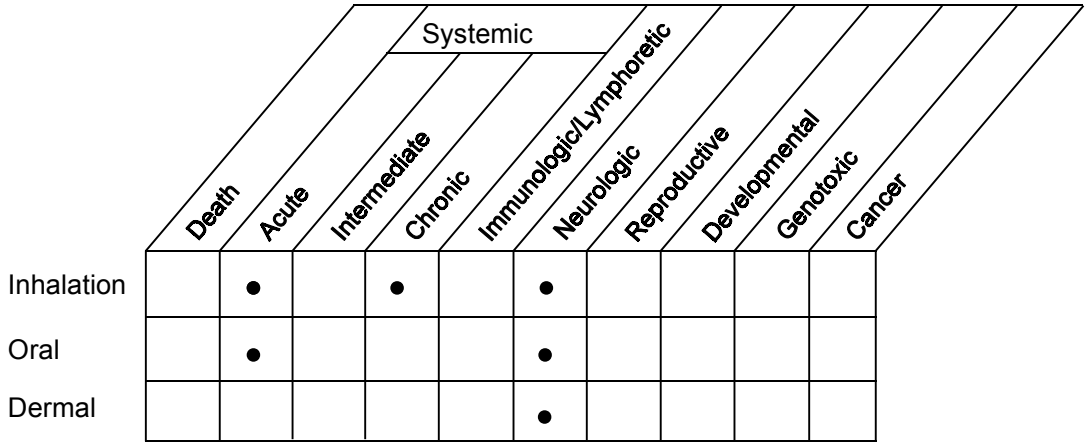
Human



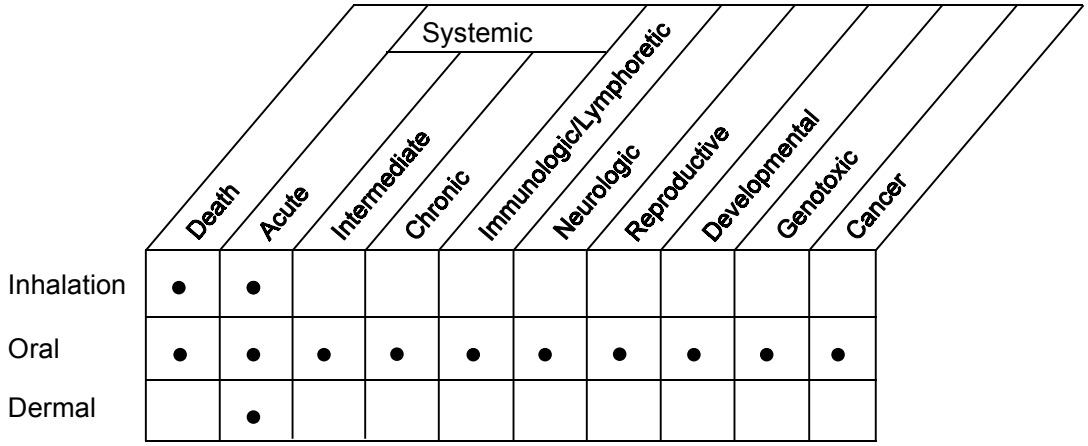
Animal

● Existing Studies

Figure 2-10. Existing Information on Health Effects of Organic Arsenic



Human



Animal

● Existing Studies

As discussed previously, in evaluating the adequacy of the database on arsenic, it is important to keep in mind that most studies in animals indicate that they are quantitatively less sensitive to arsenic than humans. For this reason, data from animal studies should be used to draw inferences about effects in humans only with caution.

2.12.2 Identification of Data Needs

Acute-Duration Exposure. There is only limited information on the effects of acute inhalation exposure to arsenic in humans, but the chief symptoms appear to be irritation of the respiratory and gastrointestinal tracts (Beckett et al. 1986; Bolla-Wilson and Bleecker 1987; Dunlap 1921; Ide and Bullough 1988; Morton and Caron 1989; Pinto and McGill 1953). Quantitative data are lacking, but effects generally appear to be mild even at high-exposure levels. On this basis, it seems that risks of acute effects are probably low for inhalation exposures in the environment or near waste sites. Research to obtain a quantitative acute inhalation NOAEL value that could be used to derive an acute inhalation MRL would, therefore, be useful but not critical. There are numerous case studies in humans on the acute oral toxicity of arsenic, and the main end points (gastrointestinal irritation, pancytopenia, hepatic injury, neuropathy) are well characterized (Armstrong et al. 1984; Fincher and Koerker 1987). A provisional acute oral MRL of 0.005 mg As/kg/day was derived for inorganic arsenic based on a LOAEL for gastrointestinal symptoms and facial edema reported by Mizuta et al. (1956). Additional studies to define an acute oral NOAEL would be useful to reduce uncertainty in the MRL derivation. Acute dermal exposure is unlikely to cause serious systemic injury, but it can lead to contact dermatitis and skin sensitization (Holmqvist 1951; Pinto and McGill 1953). However, available data do not permit a quantitative estimate of the concentration of arsenic on the skin or in air, dust, soil, or water that causes these effects. Further research would be valuable to obtain a quantitative NOAEL for direct dermal effects, since humans may have dermal contact with contaminated soil or water near hazardous waste sites.

No information was located on the acute toxicity of organic arsenicals in humans. Acute lethality and systemic toxicity data exist for several compounds by both oral and inhalation exposure of animals, and these data suggest that the organic derivatives of arsenic may cause effects similar to the inorganic forms, but only at higher doses (Kaise et al. 1989; NTP 1989b; Rogers et al. 1981; Stevens et al. 1979). Even though these compounds appear to be less toxic than inorganic arsenic, additional studies (especially in humans) would be valuable, since acute oral, inhalation, or dermal exposures may occur during manufacture or use of agricultural organic arsenicals, or at waste sites where organic arsenicals have been

deposited. Derivation would be useful, but not critical, since those coming into contact with organic arsenic compounds are regulated under OSHA and/or wear protective clothing as recommended by manufacturers.

Intermediate-Duration Exposure. Intermediate-duration inhalation exposure of humans to arsenic appears to result in respiratory tract irritation (occasionally including perforation of the nasal septum) and mild gastrointestinal tract irritation (Ide and Bullough 1988). Quantitative data are too limited (only one study, of one individual) to derive an intermediate-duration inhalation MRL. Further studies to define the NOAEL for intermediate-duration inhalation exposure of humans would be valuable, since humans could be exposed to arsenic-containing airborne dusts near smelters, chemical plants, or waste sites. Effects of intermediate-duration oral exposure are similar to those of acute oral exposure, but may also include development of vascular injury and a characteristic group of skin changes (Franzblau and Lilis 1989; Holland 1904; Wagner et al. 1979). Most studies indicate that these effects occur at doses of about 0.05 mg As/kg/day or higher, but the data do not provide a firm basis for identifying the intermediate-duration NOAEL. For this reason, no intermediate-duration oral MRL has been derived. Further studies to establish the NOAEL would be valuable, since humans could have intermediate-duration oral exposures to arsenic through ingestion of contaminated soil or water near smelters, chemical factories, or waste sites. Since dermal effects appear to be restricted to acute irritancy, intermediate-duration studies are probably not essential.

No information was located on the intermediate-duration toxicity of organic arsenicals in humans. The intermediate-duration oral toxicities of roxarsone, MMA, and DMA have been investigated in animals (Edmonds and Baker 1986; Jaghabir et al. 1989; Kerr et al. 1963; NTP 1989b; Prukop and Savage 1986; Siewicki 1981), but data are lacking for any compound by the inhalation route. Further studies on the intermediate-duration oral, inhalation, and dermal toxicity of these compounds would be valuable, especially in humans, since people may be exposed to organic arsenicals during their manufacture or use, or from materials deposited in waste sites.

Chronic-Duration Exposure and Cancer. The target tissues of chronic-duration exposure of humans to inorganic arsenic are the same as for intermediate-duration exposure for both the oral and inhalation routes. Effects of dermal exposure appear to be restricted to direct irritation of exposed surfaces. Therefore, chronic-duration studies are probably not essential for the dermal route. Quantitative data from one study identify an inhalation exposure level of about 0.1 mg As/m^3 as the LOAEL for skin changes (Perry et al. 1948), but because there are no additional supporting studies and a

NOAEL is not clearly established, a chronic-duration inhalation MRL has not been derived. Additional studies in humans to define the chronic inhalation NOAEL for dermal or other effects would be valuable, since humans may be chronically exposed to arsenic dusts in air near smelters, chemical factories, or waste sites. Chronic oral exposure data from studies in humans indicate that the LOAEL for skin lesions and other effects is probably about 0.01–0.02 mg As/kg/day (10–20 µg As/kg/day), and that the NOAEL is probably between 0.0004 and 0.0009 mg As/kg/day (0.4–0.9 µg As/kg/day) (Cebrian et al. 1983; Hindmarsh et al. 1977; Southwick et al. 1981; Tseng 1977; Tseng et al. 1968). The NOAEL of 0.0008 mg As/kg/day from the study by Tseng et al. (1968) is appropriate for derivation of a chronic-duration oral MRL, but an uncertainty factor of 3 was required to account for the fact that the population that constituted the no-effect group were relatively young (possibly decreasing the ability to detect dermal or other effects). For this reason, further epidemiological studies to provide additional support for the threshold dose for arsenic in humans would be valuable.

There are numerous studies in humans that support the carcinogenic effects of inorganic arsenic from inhalation exposure (Enterline et al. 1987a, 1987b, 1995; Jarup and Pershagen 1991; Jarup et al. 1989; Lee-Feldstein 1986; Welch et al. 1982) and oral exposure (Chen et al. 1986, 1988b, 1992; Chiou et al. 1995; Ferreccio et al. 1996; Hsueh et al. 1995; Lander et al. 1975; Liu and Chen 1996; Luchtrath 1983; Smith et al. 1992; Tseng 1977; Tseng et al. 1968; Yu et al. 1992; Zaldivar 1974; Zaldivar et al. 1981). Quantitative slope factors have been derived for both routes. There is a noticeable absence, however, of 2-year animal carcinogenicity studies for either the inhalation or oral route of exposure (Chan and Huff 1997). In light of the ongoing controversy over the reasons for the absence of a carcinogenic effect in animals, it seems prudent to firmly establish a negative effect in a 2-year study. The carcinogenic effects of chronic dermal exposure to inorganic arsenicals have not been studied, but dermal exposure is a relatively minor route of exposure, and these studies would not be a top priority.

The mechanism of arsenic carcinogenicity is not known, although the current view is that it functions mainly as a promoter. Further studies on the mechanism of arsenic toxicity would be particularly valuable to improve our ability to evaluate human cancer risks from inhalation or oral exposures that might occur near waste sites. Also, mechanistic studies could help in the evaluation of cancer risks from organic derivatives (see below).

There is very little information on the chronic toxicity of organic arsenicals. One study of workers exposed to arsanilic acid did not identify any adverse effects, but no systematic, clinical, or toxicological examinations of exposed people were performed (Watrous and McCaughey 1945). A chronic-duration

study in rats and mice given roxarsone in the diet did not reveal any obvious clinical effects (Prier et al. 1963). These data suggest that the organic arsenicals have low chronic toxicity, but further studies (especially of humans exposed during manufacture or use of organic arsenicals) would be valuable in deriving estimates of safe exposure limits.

No information was located on carcinogenic effects of organic arsenicals in humans. The carcinogenic potential of roxarsone has been investigated in rats and mice (NTP 1989b); this study detected only equivocal evidence of carcinogenicity in male rats, with no evidence of carcinogenicity in female rats or in male or female mice. However, the cancer potential for other organic arsenic compounds has not been studied in chronic bioassays. Since MMA and DMA are formed from inorganic arsenic *in vivo* by methylation in the liver, chronic studies of the carcinogenic potential of these compounds would be valuable. Studies of humans exposed in the workplace would probably be preferable to studies in animals, since animals appear to be less susceptible to the carcinogenic effects of arsenic than humans. Studies on cancer risk following chronic dermal exposure to organic arsenicals are probably not essential.

Genotoxicity. There are several studies that suggest that inorganic arsenic may cause genotoxicity (mainly chromosomal effects) in exposed humans (Burgdorf et al. 1977; Nordenson et al. 1978), and this is supported by numerous studies in animals (Datta et al. 1986; DeKnudt et al. 1986; Nagymajtenyi et al. 1985) and cultured cells (Beckman and Nordenson 1986; Casto et al. 1979; DiPaulo and Casto 1979; Lee et al. 1985; Nakamuro and Sayato 1981; Nishioka 1975; Oberly et al. 1982; Okui and Fujiwara 1986; Sweins 1983; Ulitzer and Barak 1988; Zanzoni and Jung 1980). The mechanism of genotoxicity is not known, but may be due to the ability of arsenite to inhibit DNA replicating or repair enzymes (Li and Rossman 1989) or the ability of arsenate to act as a phosphate analog. Further studies to improve our understanding of the mechanism of genotoxicity would be valuable, since this could aid in the understanding of arsenic-induced cancer risk.

Reproductive Toxicity. No information was located regarding the effect of inorganic arsenic on gametogenesis or reproductive organ pathology in humans, and few reproduction studies were located in animals. Available animal studies did not find evidence for reproductive effects following inhalation or oral exposure (Holson et al. 1999, 2000), except for a trend toward decreased pups per litter in mice in a 3-generation study (Schroeder and Mitchner 1971) that is consistent with embryolethality observed in developmental studies of inorganic arsenic. Studies on spermatogenesis and reproductive success in arsenic-exposed workers would be valuable in evaluating whether there are significant reproductive risks

of arsenic in humans, and this could be further strengthened by studies including histopathological examination of reproductive tissues (which was not done in the existing studies) in animals.

No information was located on reproductive effects of organic arsenicals in humans, but one study in animals indicated that oral exposure of male mice to MMA could result in a marked decrease in litter production in untreated females (Prukop and Savage 1986). This suggests that spermatogenesis or mating behavior may have been adversely affected, and further studies would be valuable to investigate the mechanism of this effect and whether other organic arsenicals produce similar effects.

Developmental Toxicity. There are several epidemiological studies that suggest that inhalation (Nordstrom et al. 1978a, 1978b, 1979a, 1979b) or oral (Aschengrau et al. 1989; Zierler et al. 1988) exposure to inorganic arsenic might increase the risk of low birth weight, congenital defects, or abortion in exposed women. These studies do not establish that arsenic was responsible, since all involved exposures to other chemicals or risk factors, but do suggest that additional studies on developmental parameters in humans exposed to arsenic would be valuable in determining whether this is an effect of concern. Studies in animals support the view that oral, inhalation, and parenteral exposure to inorganic arsenic can all increase the incidence of fetotoxicity and teratogenicity, although this appears to occur only at doses that are toxic or even lethal to the dams (Baxley et al. 1981; Beaudoin 1974; Carpenter 1987; Ferm and Carpenter 1968; Ferm et al. 1971; Hanlon and Ferm 1986c; Holson et al. 1999, 2000; Hood and Bishop 1972; Hood and Harrison 1982; Hood et al. 1978; Mason et al. 1989; Nagymajtenyi et al. 1985; Nemec et al. 1998; Stump et al. 1999; Willhite 1981). Thus, additional studies in animals may be useful in defining the mechanisms of these developmental effects and in identifying the time of maximum susceptibility of the fetus, but such studies probably will not help identify a safe exposure level for humans.

No information was located regarding developmental effects in humans after oral or inhalation exposure to organic arsenicals. One oral study and two intraperitoneal ingestion studies in animals indicate that MMA and DMA can produce developmental effects, but only at levels that cause maternal toxicity (Hood et al. 1982; Rogers et al. 1981; Willhite 1981). However, in view of the apparent differences in susceptibility between animals and humans, it would be valuable to investigate whether there are any measurable effects on development in humans exposed to organic arsenicals in the workplace or the environment.

Immunotoxicity. No studies were located on immunotoxic effects in humans after oral exposure to inorganic arsenic. One inhalation study in humans (Bencko et al. 1988), one oral study in animals (Kerkvliet et al. 1980), and one intratracheal instillation study in animals (Sikorski et al. 1989) suggest that arsenic causes little or no functional impairment of the immune system, but one inhalation study in animals found decreased pulmonary bactericidal activity and increased susceptibility to streptococcal infection in exposed mice (Aranyi et al. 1985). Additional studies (both in humans and animals) would be valuable to investigate this end point further. Dermal exposure of humans to high levels of arsenic dusts may cause dermal sensitization (Holmqvist 1951), but the dose and time dependence of this phenomenon are not known. Studies to determine whether dermal sensitization occurs in people with low level dermal exposures to arsenic in dust or soil, such as might occur for residents near an arsenic-containing waste site, would be valuable in assessing the significance of this effect to nonoccupationally exposed populations.

No information was located on the immunotoxicity of organic arsenicals in humans or animals. Since there are suggestions that inorganic arsenic may cause some changes in the immune system, studies on possible immune effects of the common organic arsenicals might be helpful.

Neurotoxicity. There is convincing evidence from studies in humans that inorganic arsenic can cause serious neurological effects, both after inhalation (Beckett et al. 1986; Danan et al. 1984; Morton and Caron 1989) and oral exposure (Armstrong et al. 1984; Feldman et al. 1979; Fincher and Koerker 1987; Huang et al. 1985; Landau et al. 1977; Mizuta et al. 1956; Silver and Wainman 1952). This is based mainly on clinical observations and neurological examinations of exposed persons and is confirmed by histological examination of nerve biopsy specimens. Available studies provide a reasonable estimate of LOAEL and NOAEL values by the oral route, but similar data are lacking for the inhalation route. Further studies designed to identify the threshold for neurological effects in humans exposed by the inhalation route would be valuable, since humans may be exposed to arsenic dusts in air from smelters, chemical factories, or waste sites. Animals appear to be much less susceptible than humans to the neurological effects of inorganic arsenic, so studies in animals would probably not help in estimation of a safe exposure limit.

No information was located on neurological effects of organic arsenicals in humans, but clear clinical and histological signs of neurotoxicity have been noted in pigs given repeated oral doses of roxarsone (Edmonds and Baker 1986; Kennedy et al. 1986; Rice et al. 1985). These findings suggest that more extensive investigations of the neurotoxic potential of roxarsone and other organic arsenicals would be

valuable to determine the potential human health risk from these compounds, since humans could be exposed during the manufacture or use of these compounds, or near waste sites where they have been deposited.

Epidemiological and Human Dosimetry Studies. Numerous epidemiologic studies of humans exposed to inorganic arsenic by the oral and inhalation routes constitute the database on arsenic-related cancer and noncancer human health effects. As with virtually all epidemiologic investigations, these studies are limited by possible confounding from factors such as smoking, exposure to other chemicals, and differences in population characteristics (e.g., nutritional state, metabolism, and toxicokinetics) that inhibit extrapolation of study results to a wider population. Moreover, many of these studies lack good dose estimates for study participants. Some studies lack quantitative data altogether. For this reason, improved data on confounding factors and improved methods of human dosimetry would be valuable in any further human epidemiologic studies of arsenic, either in the workplace or in the general environment. Recent work has broadened the qualitative dose-response information beyond the highly exposed Taiwanese population, but additional studies of persons with lower exposure levels would be especially valuable for risk assessments for the U.S. population. From a public health standpoint, well designed studies of common noncancer health outcomes (e.g., cardiovascular disease and diabetes) could be more important than additional studies of cancer. Availability of methods for biomonitoring of exposure are discussed below.

Biomarkers of Exposure and Effect.

Exposure. There are sensitive and specific methods for measuring arsenic in blood, urine, hair, nails, and other tissues, and this is the approach normally employed for measuring arsenic exposure in humans. Usually total arsenic is measured, but methods are available for measuring inorganic arsenic and each of the organic derivatives separately. Urinary levels are generally considered to be the most reliable indication of recent exposures (Enterline et al. 1987a; Milham and Strong 1974; Pinto et al. 1976; Polissar et al. 1990), but if a high urinary level is present, care must be taken to account for the presence of nontoxic forms of arsenic from the diet. Blood levels are sometimes used to evaluate the status of acutely poisoned individuals (Driesback 1980; Heydorn 1970; Hindmarsh and McCurdy 1986; Valentine et al. 1979, 1981), but this approach is not generally useful for biomonitoring of long-term exposure to low levels. Hair and nails provide a valuable indication of exposures that occurred 1–10 months earlier (Agahian et al. 1990; Bencko et al. 1986; Choucair and Ajax 1988; Landau et al. 1977; Milham and Strong 1974; Southwick et al. 1981; Valentine et al. 1979; Yamauchi et al. 1989), although care must be

taken to exclude external contamination of these samples. Cumulative urinary arsenic levels may be used to derive a quantitative estimate of exposure (Enterline et al. 1987a; Pinto et al. 1976), but data on the quantitative relation between exposure and arsenic levels in nails and hair were not located. Efforts to establish an algorithm for estimating past exposure levels from hair or nail levels would be valuable in quantifying average long-term exposure levels in people where repeated urinary monitoring is not feasible.

Effect. The effects of arsenic are mainly nonspecific, but the combined presence of several of the most characteristic clinical signs (e.g., nausea, diarrhea, peripheral neuropathy, anemia, vascular lesions, hyperkeratinization, hyperpigmentation) is usually adequate to suggest arsenic intoxication. Although there are standard clinical methods for detecting and evaluating each of these effects, there are no recognized methods for identifying early (preclinical) effects in exposed persons. Neurophysiological measurements of nerve conduction velocity or amplitude have been investigated (Goebel et al. 1990; Jenkins 1966; Le Quesne and McLeod 1977; Morton and Caron 1989; Murphy et al. 1981), but at present, this approach does not seem to offer much advantage over a standard neurological examination. Changes in urinary excretion levels of several heme-related metabolites appear to be a good indication of preclinical effects of arsenic toxicity in animals (Albores et al. 1989; Sardana et al. 1981; Woods and Fowler 1978; Woods and Southern 1989), but this has not been established in humans and is not specific for arsenic-induced effects. Further efforts to develop these approaches and to identify other more specific biochemical or physiological indicators of arsenic-induced effects would be very valuable in monitoring the health of persons exposed to low levels of arsenic in the environment or near waste sites.

Absorption, Distribution, Metabolism, and Excretion. Available data from toxicokinetic studies in humans reveal that arsenates and arsenites are well absorbed following both oral and inhalation exposure. Data on distribution are limited, but it appears that arsenic is transported to nearly all tissues. Metabolism involves mainly reduction-oxidation reactions that interconvert As(+5) and As(+3) and methylation of As(+3) to yield MMA and DMA. Most arsenic is rapidly excreted in the urine as a mixture of inorganic arsenics, MMA, and DMA, although some may remain bound in tissues (especially skin, hair, and fingernails). These findings are strongly supported by numerous studies in animals. Because methylation represents a detoxification pathway, an area of special interest is the capacity of the human body to methylate inorganic arsenic. Limited data suggest that the methylation system might begin to become saturated at intakes of about 0.2–1 mg As/day (Buchet et al. 1981b; Marcus and Rispin 1988), but this is uncertain. Further studies to define the rate and saturation kinetics of whole body methylation in humans would be especially helpful in evaluating human health risk from the low levels of

arsenic intake that are usually encountered in the environment. Along the same line, further studies to determine the nature and magnitude of individual variations in methylation capacity and how this depends on diet, age, and other factors would be very useful in understanding and predicting which members of a population are likely to be most susceptible.

The toxicokinetics of dermal exposure have not been studied. It is usually considered that dermal uptake of arsenates and arsenites is sufficiently slow that this route is unlikely to be of health concern (except that due to direct irritation), but studies to test the validity of this assumption would be valuable. Also, dermal uptake of organic arsenicals could be of concern, and quantitative data on the rate and extent of this would be helpful in evaluating risks from application of arsenical pesticides or exposures to organic arsenicals in waste sites.

Comparative Toxicokinetics. Available toxicity data indicate that arsenic causes many of the same effects in animals that are observed in humans, but that animals are significantly less sensitive. The basis for this difference in susceptibility is not certain but is probably mainly a result of differences in absorption, distribution, metabolism, or excretion. For example, rats strongly retain arsenic in red blood cells (Lanz et al. 1950), while humans (and most other species) do not. Similarly, marmoset monkeys do not methylate inorganic arsenic (Vahter and Marafante 1985; Vahter et al. 1982), while humans and other animal species do. Because of these clear differences in toxicity and toxicokinetics between species, further comparative toxicokinetic studies that focus on the mechanistic basis for these differences would be very valuable. At a minimum, this would help clarify which laboratory species are the most useful models for humans and could ultimately lead to development of a physiologically based pharmacokinetic model that would permit reliable extrapolation of observations across species.

Methods for Reducing Toxic Effects. There are a number of general methods for reducing the absorption of arsenic in the gastrointestinal tract and skin, but there are currently no methods for reducing the absorption of arsenic from the lungs. The removal of arsenic from the gastrointestinal tract is usually facilitated by the use of emetics, cathartics, lavages, or activated charcoal (Aposhian and Aposhian 1989; ATSDR 1990; Campbell and Alvarez 1989; Driesback 1980; Ellenhorn and Barceloux 1988; EPA 1989e; Haddad and Winchester 1990; Stutz and Janusz 1988). Studies that investigate the effects of phosphate-binding chemicals (aluminum hydroxide) and nonabsorbable sulfhydryl compounds on the absorption of pentavalent and trivalent arsenic, respectively, may be useful in developing treatments which are more specific to arsenic intoxication. Once arsenic is in the body, treatment usually involves the use of one or more chelators, such as BAL or penicillamine. However, these agents often exhibit adverse side effects

(ATSDR 1990; Ellenhorn and Barceloux 1988). Further studies investigating the efficacy of less toxic arsenic chelators, such as DMSA, DMPA, DMPS, and N-acetyl cysteine, may lead to the development of safer treatment methods. Studies on the efficacy of chelators in treatment of chronic arsenic exposure would also be helpful. Trivalent arsenic is generally believed to exert toxic effects by binding to the sulfhydryl group of key enzymes, thereby interfering with a number of biological processes, such as gluconeogenesis and DNA repair (Li and Rossman 1989; Szinicz and Forth 1988). Since pentavalent arsenic may need to be reduced in the body to the trivalent state before it can exert toxic effects, studies that investigate methods for blocking this conversion may lead to a method for interfering with the mechanism of action for pentavalent arsenic.

Children's Susceptibility A majority of the data on the effects of exposure of humans to arsenic has focused on adults. Although a few studies of acute poisoning and chronic exposure specifically describe children (Borgono et al. 1980; Foy et al. 1992; Kersjes et al. 1987; Rosenberg 1974; Zaldivar 1974; Zaldivar and Guillier 1977), in general, data are lacking. Specifically, although there is a substantial database on the effect of arsenic on animal development, there are few data describing developmental effects in humans. Additional research in this area, using populations in areas of endemic arsenic exposure, would be useful.

Although there is no reason to suspect that the pharmacokinetics of arsenic differs in children and adults, there are few data available on this topic. Research on absorption, distribution, metabolism, and excretion in children would aid in determining if children are at an increased risk, especially in areas where chronic exposure to an environmental source occurs. With regard to exposure during development, additional research on maternal kinetics, and transfer via breast milk would be useful in obtaining a more complete picture of prenatal and neonatal development, especially with regard to neural development and the possible development of childhood cancer.

2.12.3 Ongoing Studies

A number of researchers are continuing to investigate the toxicity and toxicokinetics of arsenic. Table 2-16 summarizes studies being sponsored by agencies of the U.S. federal government. Additional research is being sponsored by industry groups and other agencies, and research is also ongoing in a number of foreign countries. Some of these studies are listed in Table 2-17.

Table 2-16. Ongoing Studies on Health Effects of Arsenic, Federally Funded

Investigator	Affiliation	Title	Sponsor
Aposhian, H Vasken	University of Arizona, Tucson, Arizona	Detoxification of metals—*in vitro* and *in vivo* studies	NIEHS
Bayse, Gladys S	Spelman College, Atlanta, Georgia	Biotransformation of the feed additives roxarsone and arsanilic acid	National Institute of General Medical Sciences
Benjamin, Stephen A	Colorado State University, Fort Collins, Colorado	Chemical mixtures as promoters of hepato-carcinogenesis	NIEHS
Billings, Ruth E	Colorado State University, Fort Collins, Colorado	Mechanisms of toxic chemical interaction in the liver—hepatotoxicity	NIEHS
Block, Gladys	University of California, Berkeley, California	Nutrition, environment interactions	NIEHS
Capra, J Donald	Oklahoma Medical Research Foundation, Oklahoma City, Oklahoma	Immunoglobulin V region structures—genetic implications	National Institute of Allergy and Infectious Diseases
Carter, Dean E	University of Arizona College of Pharmacy, Tucson, Arizona	Arsine metabolism and mechanism of toxicity	NIEHS
Checkoway, Harvey	University of Washington, Seattle, Washington	Environmental and biochemical risk factors for Parkinson's disease	NIEHS
Chou, Billy J	Battelle Pacific Northwest Laboratories	Isoprene, indium phosphide, gallium arsenide	NIEHS
Finnell, Richard H	Texas A & M University College Station, Texas	Folate receptor knockouts, arsenate and birth defects	National Institute of Child Health and Human Development
Gandolfi, A Jay	University of Arizona, Tucson, Arizona	Metal-metal interactions in the kidney	NIEHS
Germolec, D R	NIEHS, NIH	Effects of environmental pollutants and therapeutics on the immune	NIEHS
Hall, Eric H	Columbia University, New York, New York	Quantitative studies of oncogenic transfection	National Cancer Institute
Hamilton, Joshua W	Dartmouth College, Hanover, New Hampshire	Molecular basis for effects of carcinogenic metals on inducible gene expression	NIEHS
Holbrook, N J	NIA, NIH	Regulation and function of the putative transcription factor GADD153	National Institute on Aging

Table 2-16. Ongoing Studies on Health Effects of Arsenic, Federally Funded *(continued)*

Investigator	Affiliation	Title	Sponsor
Howell, Stephen B	University of California San Diego, California	Molecular pharmacology of platinum drug resistance	National Cancer Institute
Hunter, David	Harvard School of Public Health, Boston, Massachusetts	Arsenic exposure and skin and bladder cancer	NIEHS
Karagas, M	Dartmouth College, Hanover, New Hampshire	Epidemiology of arsenic and other toxic metals	NIEHS
Kochhar, TS	Kentucky State University, Frankfort, Kentucky	Induction of chromosome changes in mammalian cells	National Institute of General Medical Sciences
McCoy, Kathleen L	Virginia Commonwealth University, Richmond, Virginia	Gallium arsenide suppression of antigen processing	NIEHS
Nielsen FH, Hunt CD, Uthus EO	Agricultural Research Service, Grand Forks, North Dakota	Biochemical, physiological, and nutritional roles of certain ultratrace elements	USDA, Agricultural Research Service
Nielsen FH, Uthus EO, Hunt CD	Agricultural Research Service, Grand Forks, North Dakota	Biochemistry and metabolism of certain ultratrace elements	USDA, Agricultural Research Service
Pott, Wendy A	Colorado State University, Foothills Campus, Fort Collins, Colorado	Arsenic containing mixtures in angiosarcoma induction	National Cancer Institute
Pritsos CA	University of Nevada, Reno, Nevada	Environmental transformation, exposure and effects of pesticide residues	USDA, Cooperative State Research Svc
Ron, David	New York University Medical Center Skirball Institute Lab 9 New York, New York	Cellular response to nonmutagenic carcinogens	NIEHS
Shelburne, John D, M.D., Ph.D.	Department of Veterans Affairs, Medical Center, Durham, North Carolina	*In vitro* and *in vivo* effects of sodium arsenite and sodium arsenate on organelle function, and element composition of proximal tubules	Department of Veterans Affairs, Research and Development

Table 2-16. Ongoing Studies on Health Effects of Arsenic, Federally Funded *(continued)*

Investigator	Affiliation	Title	Sponsor
Silver, S	University of Illinois at Chicago, Department of Microbiology and Immunology	Oxidation and reduction of arsenic oxyanions: a molecular genetics, biochemistry, and microbiological approach	USDOE Energy Research
Smith, Allan	University of California, Berkeley, California	Mutagenesis and carcinogenesis	NIEHS
Smith, Allan H	University of California, Berkeley, California	Bladder cancer case control study of arsenic in water	NIEHS
Smith, Allan H	University of California, Berkeley, California	Arsenic biomarker epidemiology	NIEHS
Smith, Allan H	University of California, Berkeley, California	A dose-response and susceptibility investigation of skin keratoses and hyperpigmentation due to ingestion of arsenic in drinking water	EPA
Smith, Karol R	Dartmouth College, Hanover, New Hampshire	As(iii) enhances AP 1 activity via c jun phosphorylation	NIEHS
Snow, Elizabeth T	New York University Medical Center, New York, New York	Arsenic-glutathione interactions and skin cancer	EPA
Styblo, Miroslav	University of North Carolina, Chapel Hill, North Carolina	Arsenicals, glutathione reductase and cellular redox status	EPA
Tannenbaum, Steven R	Massachusetts Institute of Technology, Cambridge, Massachusetts	Proteins and DNA—new methods of adduct detection	NIEHS
Taylor, PR	NCI, NIH	Biologic specimen bank for early lung cancer markers in Chinese tin miners	Division of Cancer Prevention and Control
Thilly, William G	Massachusetts Institute of Technology, Cambridge, Massachusetts	Human peripheral blood studies of mutations in the Aberjona region	NIEHS
Thilly, William G	Massachusetts Institute of Technology, Cambridge, Massachusetts	Human cell culture studies of mutagens in the Aberjona Basin	NIEHS

Table 2-16. Ongoing Studies on Health Effects of Arsenic, Federally Funded *(continued)*

Investigator	Affiliation	Title	Sponsor
Warrell, Raymond P, Jr	Sloan Kettering Institute Cancer Research, New York, New York	Arsenic trioxide in acute promyelocytic leukemia	National Cancer Institute
Yang, Raymond SH	Colorado State University, Fort Collins, Colorado	Toxicological interaction studies in chemical mixtures—pharmacokinetics	NIEHS

EPA = Environmental Protection Agency; NCI = National Cancer Institute; NIA = National Institute on Aging; NIEHS = National Institute of Environmental Health Sciences; NIH = National Institute of Health; USDA = U.S. Department of Agriculture; USDOE = U.S. Department of Energy

Table 2-17. Ongoing Studies on Health Effects of Arsenic with Industry, Foreign, and Other Agency Funding*

Investigator	Research description
Aposhian et al. 1989	Biodiversity of organic arsenite methyltransferases
Ayala-Fierro and Carter 1998	Arsenic vs arsenite toxicity in different cell types
Bajenova et al. 1998	Effects of the heavy metals chromium and arsenic on hormone-inducible expression of PEPCK/luciferase genetic constructs
Beck and Slayton 1998	Impact of arsenic (As_i) metabolism on human populations: Dose response relationships in arsenic-induced cancers
Bencko 1997	Contribution to neurotoxicity of arsenic in environmental settings
Brown and Kitchin 1998	Arsenic carcinogenesis: dimethylarsinic acid causes rat pulmonary DNA damage
Calleha et al. 1997	Arsenic trioxide induces apoptosis in K562 chronic myelogenous leukemia (CML) cells
Dai et al. 1997	Induction of apoptosis by the combined activity of arsenic trioxyde (As_2O_3) and ascorbic acid (AA) in (14;18) B-cell lymphoma
Das et al. 1997	Bio-anticlastogenic effects of mustard oil and garlic in the first-generation offspring of sodium arsenite treated mice
Del Razo et al. 1998	Impact of arsenic metabolism on human populations: Metabolism of arsenic and sensitivity to carcinogenesis in humans
Di Noto et al. 1997	*In vitro* treatment of APL cells with arsenic trioxide (As_2O_3) results in a highly specific induction of solitary CD66c display
Fortoul et al. 1998	Ultrastructural changes in human lymphocytes challenged with sodium arsenite
Gabrilove et al. 1997	Effects of arsenicals in chronic leukemias
Gailer and Aposhian 1998	The detection of a novel arsenic-selenium compound
Gilani 1997	Teratogenicity of metals to chick embryos
Gonsebatt et al. 1996	Genotoxicity of arsenic exposure
Hamadeh et al. 1998	Arsenic species and gene activation in human lymphoblastoid cells
Harrington-Brock et al. 1998	Biological effects of arsenic exposure: *in vitro* and *in vivo*
He et al. 1997	Therapeutic trials with retinoic acid and arsenic trioxyde (As_2O_3) in PML-RARα and ZF-RARα transgenic mice as models of APL
Hu Yu and Snow 1998a	Effect of arsenic on DNA ligase activity in human cells in culture
Hu Yu and Snow 1998b	Arsenic-GSE interactions: modulation of cellular redox levels and signal transduction pathways
Huang et al. 1997	Potentiation of arsenic trioxyde (As_2O_3) induced apoptosis by retinoic acid (RA) in RA-sensitive (S) and RA-resistant (R) HL-60 myeloid leukemia cells

Table 2-17. Ongoing Studies on Health Effects of Arsenic with Industry, Foreign and Other Agency Funding* *(continued)*

Investigator	Research description
Hueges de Thé et al. 1997	Arsenic and retinoic acid: towards rational treatments of acute promyelocytic leukemia
Hunter and Dix 1996	Antisense oligonucleotides against *Hsp70-1* and *70-3* increase mouse embryonic sensitivity to arsenite-induced dysmorphogenesis *in vitro*
Ishitsuka et al. 1997	Arsenic acid as well as retinoic acids have therapeutic potential to adult T-cell leukemia
Kaltreider et al. 1998	Effects of the heavy metals arsenic and chromium on transcription factor binding and gene expression
Kato et al. 1997	Modulation of the stress-induced synthesis of stress proteins by reducing reagents: stimulation and suppression
Kinjo et al. 1997	Establishment of a retinoic acid resistant human APL model in hGM-CSF transgenic SCID mice and their application to the *in vivo* study of arsenic trioxyde (As_2O_3)
Lehmann et al. 1997	Arsenic trioxyde (As_2O_3) induces apoptosis and cytotoxic effects in blast cells from patients with non-M3 AML
Li and Broome 1997a	Differential cytotoxicity of As_2O_3 and arsenic azoproteins on leukemic cells
Li and Broome 1997b	Apoptosis induced in premyelocytic leukemia cells by arsenic and proteasome inhibitors
Ma Jun et al. 1997	Clincal observation on arsenic trioxide in the treatment of acute promyelocytic leukemia
Mass 1998	Mechanisms of arsenic induced cancer: A role for hypermethylation
McDorman et al. 1998	Micronucleus analysis in mice chronically exposed to arsenic in drinking water
Menendez et al. 1998	Induction of p53 protein expression by sodium arsenite
Ostrosky-Wegman et al. 1998	Modulation of p53 function by arsenic and its role in cell cycle impairment
Peraza et al. 1998	Lack of dimethyl arsenic hepatotoxicity to 6-week old male Fischer 344 rats
Peters et al. 1998	Application of *in vitro* bioaccessibility test data to a public health risk assessment of arsenic-contaminated soils
Pott et al. 1998	Inhibitory effects of arsenic-containing mixtures in a multiple organ carcinogenicity bioassay
Rousselot et al. 1997	Arsenic trioxyde (As_2O_3) and Melarsoprol induce myeloma cell apoptosis *in vitro* with a preferential effect on tumoral cells in patients' bone marrow
Schoof and Evans 1998	Use of background arsenic exposure data to assess health significance of exposures to arsenic in soil
Shao et al. 1997	An APL subclone with a dominant negative PML/RARA mutation that resists retinoid degradation undergoes loss of PML-RARA protein and apoptosis in response to arsenic

Table 2-17. Ongoing Studies on Health Effects of Arsenic with Industry, Foreign and Other Agency Funding* *(continued)*

Investigator	Research description
Shipp et al. 1998	Application of the risk assessment approaches in EPA proposed cancer guidelines to arsenic
Smith et al. 1998	Evaluation of carcinogenic potential of chemical mixtures containing arsenic and volatile organics in SHE cells
Steinberg et al. 1997	Low dose chronic treatment of human keratinocytes with inorganic arsenic causes hyperproliferation and altered protein phosphorylation
Su et al. 1997	Arsenic is cytotoxic at micromolar concentration, but does not inhibit purified human DNA repair enzymes at less than millimolar concentrations
Susten et al. 1998	An integrated approach to estimating total arsenic exposure in humans
Swanson and Angle 1998	Increased cellular homocysteine (Hcy) as a mechanism for the proliferative responses of cobalamin (B12) dependent human fibroblasts to arsenic (As3+)
Thomas and Herbin-Davis 1998	Characteristics of the accumulation of arsenic (As) by arsenate (As^{v})-exposed rabbit erythrocytes
Tong and Xu 1998	Peripheral neuropathy, skin damage and liver abnormalities in miners with long-term exposure to arsenic
Trouba et al. 1998	Long-term modulation of mitogen activated protein kinase following sodium arsenite exposure
Turck et al. 1998	Assessment of the developmental toxicity of sodium monofluoroacetate (1080) in rats
Vargas et al. 1998	Activation of transcription factors by sodium arsenite in human lymphocytes
Vega 1996	Sodium arsenite effects on interleukin 2 secretion
Waalkes and Zhao 1998	The association of arsenic-induced malignant transformation with DNA hypomethylation and aberrant gene expression
Wang et al. 1997	Arsenic trioxyde and melarsoprol induce programmed cell dath in myeloid leukemia cell lines and function in a PML and PML/RARα independent manner
Westervelt et al. 1997	Response and toxicity associated with dose excalation of arsenic trioxide in the treatment of resistant acute promyelocytic leukemia
Wildfang et al. 1998	Hamster and rabbit arsenite and MMA methyltransferase kinetics: comparisons of *in vitro* properties
Xie et al.1997	Melarsoprol and arsenic trioxide increase cell death on doxorubicin-resistant human leukemia and myeloma cells by regulating expression of BCL-2 apoptosis regulatory family
Yamauchi et al. 1998	Metabolism and biological monitoring of arsenic poisoning following chronic arsenic exposure in Inner Mongolia, China

Table 2-17. Ongoing Studies on Health Effects of Arsenic with Industry, Foreign and Other Agency Funding* *(continued)*

Investigator	Research description
Zakharyan et al. 1998	Purification and properties of the arsenite methylating isoenzymes of rabbit liver
Zhao et al. 1998	Role of c-myc overexpression in arsenic-induced malignant transformation
Zheng et al. 1998	Molecular alterations in renal cortical slices following exposure to sub-toxic levels of arsenite

* Research found in the open literature, not identified in the Federal Research in Progress database

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

Arsenic appears in Group V of the periodic table. It exists in four oxidation states: -3, 0, +3, and +5. Table 3-1 summarizes information on the chemical identity of elemental arsenic and some common inorganic compounds of arsenic. The corresponding information for several common organic arsenic compounds is presented in Table 3-2.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Table 3-3 summarizes important physical and chemical properties of elemental arsenic, As(0), and some common inorganic arsenic compounds. As(0) occurs as two allotropic forms, yellow and metallic gray. The metallic gray form is the stable form under ordinary conditions. The corresponding information for several common organic arsenic compounds is presented in Table 3-4.

Table 3-1. Chemical Identity of Arsenic and Selected Inorganic Arsenic Compounds[a]

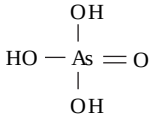
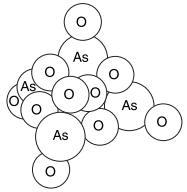
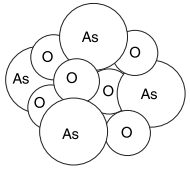
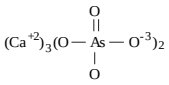
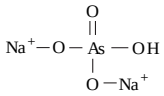
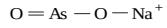
Characteristic	Arsenic	Arsenic acid	Arsenic pentoxide	Arsenic trioxide
Synonym(s)	Arsenic black; colloidal arsenic; gray arsenic	Orthoarsenic acid	Arsenic (V) oxide; arsenic acid anhydride; diarsenic pentoxide	Arsenic oxide; arsenious acid; arsenious oxide; white arsenic
Registered trade name(s)	No data	Dessican L-10®[b]; Scorch®[b]	No data	Arsenolite®[c]; Claudelite®[c]
Chemical formula	As	H_3AsO_4	$As_2O_5(As_4O_{10})$	$As_2O_3(As_4O_8)$
Chemical structure	As			
Identification numbers:				
CAS registry	7440-38-2	7778-39-4	1303-28-2	1327-53-3
NIOSH RTECS	CG0525000	CG070000	CG2275000	CG3325000
EPA hazardous waste	D004	D004, P011	D004, P011	D004, P012
OHM/TADS	No data	No data	No data	No data
DOT/UN/NA/IMCO shipping	UN1558/ IMCO 6.1	UN1553 (liquid) UN1554 (solid) / IMCO 6.1	UN1559/ IMCO 6.1	UN1561/ IMCO 6.1
HSDB	509	431	429	419
NCI	No data	No data	No data	No data

Table 3-1. Chemical Identity of Arsenic and Selected Inorganic Arsenic Compounds[a] (*continued*)

Characteristic	Calcium arsenate	Gallium arsenide	Disodium arsenate	Sodium arsenite
Synonym(s)	Calcium orthoarsenate; arsenic acid, calcium salt	Gallium monoarsenide	Sodium arsenate, dibasic; Disodium hydrogen arsenate; arsenic acid, disodium salt	Arsenious acid, sodium salt; sodium metaarsenite
Registered trade name(s)	Pencal®[b]; Spra-cal®[c]	No data	No data	Atlas A®[b]; Chem Sen®[b]; Kill-All®[b]
Chemical formula	$Ca_3(AsO_4)_2$	GaAs	Na_2HAsO_4	$NaAsO_2$[d]
Chemical structure		Ga:As		
Identification numbers:				
CAS registry	7778-44-1	1303-00-0	7778-43-0	7784-46-5
NIOSH RTECS	CG0830000	LW8800000	CG0875000	CG3675000
EPA hazardous waste	D004	No data	No data	No data
OHM/TADS	No data	No data	No data	7800057
DOT/UN/NA/IMCO shipping	UN1537 / IMCO 6.1	No data	No data	UN1686 (liquid) UN2027 (solid) / IMCO 6.1
HSDB	1433	4376	1675	693
NCI	No data	No data	No data	No data

[a]All information obtained from HSDB 1990, except where noted.
[b]Sittig 1980
[c]IARC 1980
[d]Sax and Lewis 1989
[e]Cotton and Wilkinson 1972

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

Table 3-2. Chemical Identity of Selected Organic Arsenic Compounds[a]

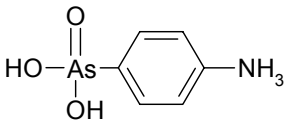
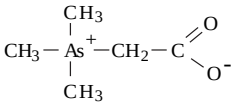
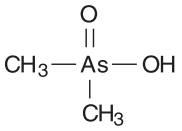
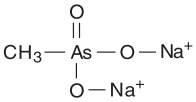
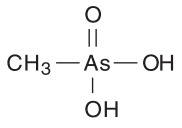
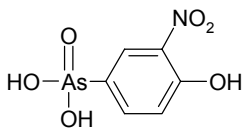
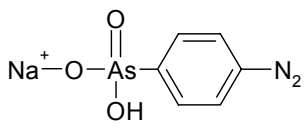
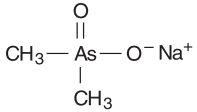
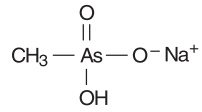
Characteristic	Arsanilic acid	Arsenobetaine	Dimethylarsinic acid	Disodium methanearsonate
Synonym(s)	4-(Aminophenyl)arsonic acid; atoxylic acid[b]	Fish arsenic	Cacodylic acid; hydroxydimethyl-arsine oxide[b]; DMA; DMAA;	DSMA[c]; disodium monomethane arsonate[b]
Registered trade name(s)	Premix®[d] Pro Gen®[d]	No data	Ansar®[c]; Arsan®[c] Silvisar®[c]; Phytar®[c]	Crab-E-Rad®[c]; Metar®[c] Sodar®[c]
Chemical formula	$(C_6H_4NH_2)H_2AsO_3$	$(CH_3)_3As^+CH_2CO_2^-$	$(CH_3)_2As(O)OH$[f]	$CH_3Na_2AsO_3$[b]
Chemical structure				
Identification numbers:				
CAS registry	98-50-0[b]	64436-13-1	75-60-5[b]	144-21-8
NIOSH RTECS	CF7875000	No data	CH7525000	PA2275000
EPA hazardous waste	No data	No data	No data	K084; K101; K102
OHM/TADS	No data	No data	No data	No data
DOT/UN/NA/IMCO shipping	No data	No data	No data	UN1556 (liquid) UN1557 (solid)
HSDB	432	No data	160	1701
NCI	No data	No data	No data	No data

Table 3-2. Chemical Identity of Selected Organic Arsenic Compounds[a] *(continued)*

Characteristic	Methanearsonic acid	3-Nitro-4-hydroxy-phenylarsonic acid	Sodium arsanilate	Sodium dimethylarsinate	Sodium methanearsonate
Synonym(s)	Arsonic acid, methyl-; monomethylarsonic acid[b]	4-Hydroxy-3-nitro-phenylarsonic acid; 3-Nitro-10; roxarsone	Arsanilic acid, sodium salt; sodium amino-arsenate; sodium p-aminophenyl-arsenate[b]	Sodium cacodylate; cacodylic acid, sodium salt; sodium dimethyl arsonate[b]	MSMA[c] ; monosodium methanearsenate[b]
Registered trade name(s)	No data	No data	Arsamin[b]	Sivisar®; Ansar; Pyntar®	Bueno®c; Daconate®c Phybane®c
Chemical formula	$CH_3H_2AsO_3$	$(C_6H_3OHNO_2)H_2AsO_3$	$(C_6H_4NH_2)NaHAsO_3$	$(CH_3)_2NaAsO_2$	$CH_3NaHAsO_3$
Chemical structure					
Identification numbers:					
CAS registry	124-58-3[b]	121-19-7[b]	127-85-5[b]	124-65-2[b]	2163-80-6[e]
NIOSH RTECS	PA1575000	CY5250000	CF9625000	CH7700000	8A2625000
EPA hazardous waste	K031	No data	No data	No data	No data
OHM/TADS	No data	No data	No data	No data	No data
DOT/UN/NA/IMCO shipping	No data	No data	No data	IMCO 6.1 / UN1688	No data
HSDB	845	4296	5189	731	754
NCI	No data	No data	No data	No data	No data

[a]All information obtained from HSDB 1998, except where noted.
[b]Merck 1989
[c]Sittig 1980
[d]IARC 1980
[e]EPA 1982d

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

Table 3-3. Physical and Chemical Properties of Arsenic and Selected Inorganic Arsenic Compounds[a]

Property	Arsenic	Arsenic acid	Arsenic pentoxide	Arsenic trioxide
Molecular weight	74.92	150.95[b]	229.84	197.84
Color	Gray	White	White	White[c]
Physical state	Solid	Solid	Solid	Solid[c]
Melting point	817 EC at 28 atm	35.5 EC	Decomposes at 315 EC	312.3 EC
Boiling point	613 EC sublimes	Loses H_2O at 160 EC	No data	465 EC[c]
Density[g]	5.727 g/cm^3	2.0–2.5 g/cm^3	4.32 g/cm^3	3.738 g/cm^3
Odor	Odorless[e]	No data	No data	Odorless[d]
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water	Insoluble	3,020 g/L at 12.5 EC	1,500 g/L at 16 EC 767 g/L at 100 EC	37 g/L at 20 EC 115 g/L at 100 EC
Organic solvent(s)	No data	Soluble in alcohol	Soluble in alcohol	Slightly soluble in alcohol[e]
Acids	Soluble in nitric acid	No data	Soluble in acid[d]	Soluble in hydrogen chloride[e]
Partition coefficients:				
Log K_{ow}	No data	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data
Vapor pressure	1 mm Hg at 373 EC[d] 40 mm Hg at 483 EC[d] 100 mm Hg at 518 EC[d]	No data	No data	66.1 mmHg at 312 EC[d]
Henry's law constant at 24.8 EC	No data	No data	No data	No data
Autoignition temperature	No data	No data	No data	Nonflammable[d]
Flashpoint	No data	No data	No data	No data
Flammability limits in air	No data	No data	No data	No data
Conversion factors: ppm (v/v) to mg/m^3 in air at 25 EC mg/m^3 to ppm (v/v) in air at 25 EC	No data	No data	No data	No data
Explosive limits	No data	No data	No data	No data
Valence states	0[e]	+5[e]	+5[e]	+3[e]

Table 3-3. Physical and Chemical Properties of Arsenic and Selected Inorganic Arsenic Compounds[a] *(continued)*

Property	Calcium arsenate	Gallium arsenide	Disodium arsenate	Sodium arsenite
Molecular weight	398.08	144.64	185.91[c]	129.91
Color	Colorless[f]	Dark gray	No data	Gray-white
Physical state	Solid	Solid	Solid[c]	Solid
Melting point	No data	1238 EC	No data	No data
Boiling point	No data	No data	No data	No data
Density[g]	3.62 g/cm^3	5.31[c] g/cm^3	1.87[c,h] g/cm^3	1.87 g/cm^3
Odor	Odorless[d]	No data	Odorless[d]	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water	0.13 g/L at 25 EC	No data	Soluble in water, glycerol[c,h]	Very soluble
Organic solvents	Insoluble	No data	Slightly soluble in alcohol[c,h]	Slightly soluble in alcohol
Acids	Soluble in dilute acids[d]	No data	No data	No data
Partition coefficients:				
Log K_{ow}	No data	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data
Vapor pressure at 25 EC	No data	No data	No data	No data
Vapor pressure at 30 EC	No data	No data	No data	No data
Henry's law constant at 24.8 EC	No data	No data	No data	No data
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits in air	No data	No data	No data	No data
Conversion factors: ppm (v/v) to mg/m^3 in air at 25 EC mg/m^3 to ppm (v/v) in air at 25 EC	No data	No data	No data	No data
Explosive limits	No data	No data	No data	No data
Valence states	+5[e]	-3	+5	+3

[a]All information obtained from Weast 1985, except where noted.
[b]Value for H_3AsO_4 - ½ H_2O
[c]Merck 1989
[d]HSDB 1990
[e]EPA 1982d
[f]Sax and Lewis 1989
[g]When a property is a function of temperature, the temperature is at room temperature unless otherwise specified.
[h]Heptahydrate

Table 3-4. Physical and Chemical Properties of Selected Organic Arsenic Compounds[a]

Property	Arsenilic acid	Arsenobetaine	Dimethylarsinic acid	Disodium methanearsonate
Molecular weight	217.06[b]	178.06[c]	138.00[d]	183.9[e]
Color	White[c]	No data	Colorless[c]	Colorless[c]
Physical state	Solid	Solid[c]	Solid[f]	Solid[c]
Melting point	232 EC[b]	204–210 EC[c]	195–196 EC[f]	>355 EC[c]
Boiling point	Loses H_2O at 15 EC[c] sublimes	No data	No data	No data
Density	1.9571[c] g/cm^3	No data	No data	No data
Odor	Practically odorless[c]	No data	Odorless[c]	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water	Very soluble in hot water[b]	No data	660 g/L at 25 EC[g]	1,000 g/L[c]
Organic solvent(s)	Soluble in alcohol; Insoluble in ether[c]	Soluble in alcohol[b]	Very soluble in alcohol[d]	Slightly soluble in alcohol[b]
Acids	Slightly soluble in acetic acid[c]	No data	Very soluble in acetic acid[f]	No data
Partition coefficients:				
Log K_{ow}	No data	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data
Vapor pressure	No data	No data	No data	No data
Henry's law constant at 24.8 EC	No data	No data	No data	No data
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits in air	No data	No data	No data	No data
Conversion factors: ppm (v/v) to mg/m^3 in air at 25 EC mg/m^3 to ppm (v/v) in air at 25 EC	No data	No data	No data	No data
Explosive limits	No data	No data	No data	No data
Valence states	+5	+5	+5	+5

Table 3-4. Physical and Chemical Properties of Selected Organic Arsenic Compounds[a] *(continued)*

Property	Methane arsonic acid	3-Nitro-4-hydroxy-phenylarsonic acid	Sodium arsanilate	Sodium dimethylarsinate	Sodium methanearsonate
Molecular weight	139.97[g]	263.03[c]	239.05[b]	159.98[f]	161.96[c]
Color	White	Pale yellow	White[b]	Colorless[c]	No data
Physical state	Solid	Solid[c]	Solid[b]	Solid[f]	No data
Melting point	161 EC[f]	No data	No data	200 EC[c]	115–119 EC[h]
Boiling point	No data	No data	No data	No data	No data
Density	No data	No data	No data	No data	No data
Odor	No data	No data	Odorless[b]	Slight odor[f]	No data
Odor threshold:					
Water	No data	No data	No data	No data	No data
Air	No data	No data	No data	No data	No data
Solubility:					
Water	Soluble[d]	Slightly soluble[c]	Soluble[b]	830 g/L at 22 EC[h]	570 g/L at 25 EC[h]
Organic solvents	Soluble in alcohol[d]	Soluble in alcohol, acetone[c]	Slightly soluble in alcohol[b]	No data	No data
Acids	No data	Soluble in acetic acid[c]	No data	No data	No data
Partition coefficients:					
Log K_{ow}	No data	No data	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data	No data
Vapor pressure at 25 EC	No data	No data	No data	No data	No data
Vapor pressure at 30 EC	No data	No data	No data	No data	No data
Henry's law constant at 24.8 EC	No data	No data	No data	No data	No data
Autoignition temperature	No data	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data	No data
Flammability limits in air	No data	No data	No data	No data	No data
Conversion factors:	No data	No data	No data	No data	No data
Explosive limits	No data	No data	No data	No data	No data
Valence states	+5	+5	+5	+5	+5

[a]All information obtained from Weast 1985, except where noted.
[b]Sax and Lewis 1989
[c]HSDB 1990
[d]Lide 1996
[e]IARC 1980
[f]Merck 1989
[g]Hood 1985
[h]EPA 1982c

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

Arsenic is the 20th most abundant element in the earth's crust. It occurs most often as the sulfide in a variety of complex minerals containing copper, lead, iron, nickel, cobalt, and other metals (Merck 1989; US Fish and Wildlife Service 1988).

Arsenic is presently obtained as a byproduct of the smelting of copper, lead, cobalt, and gold ores. Arsenic trioxide is volatilized during smelting and accumulates in the flue dust, which may contain up to 30% arsenic trioxide. The crude flue dust is further refined by mixing with small amounts of galena or pyrite to prevent the formation of arsensites and roasting to yield a arsenic trioxide of 90–95% purity. By successive sublimations, a purity of 99% can be obtained. Arsenic metal can be prepared by the reduction of arsenic oxide with charcoal. Demand for metallic arsenic is limited and thus about 95% of arsenic is marketed and consumed in combined form, principally as arsenic trioxide which is subsequently converted to arsenic acid (Carapella 1992; Hanusch et al. 1985; USGS 1998b).

Since 1985, when the ASARCO smelter in Tacoma, Washington ceased operation, there has been no domestic production of arsenic and consequently, the United States remains entirely dependent on imports (USGS 1998b; U.S. Bureau of Mines 1988, 1990). Prior to its cessation, U.S. production of arsenic trioxide had been 7,300 metric tons in 1983, 6,800 metric tons in 1984, and 2,200 metric tons in 1985 (U.S. Bureau of Mines 1988). Arsenic is recovered from nonferrous ores or concentrated in at least 18 countries. In 1998, the world’s largest producer of arsenic trioxide was China, followed by Chile, Ghana, Mexico, and France (USGS 1999b). China accounts for near all of the commercial-grade (99%-pure) arsenic metal production. The United States, with an apparent demand of more than 30,000 metric tons (60 million pounds) in 1998, is believed to be the worlds largest consumer of arsenic.

Table 4-1 lists facilities in each state that manufacture or process arsenic, the intended use, and the range of maximum amounts of arsenic that are stored on site. There are currently 52 large facilities that produce or process arsenic in the United States. The data listed in Table 4-1 are derived from the Toxics Release Inventory (TRI97 1999). Only certain types of facilities were required to report. Therefore, this is not an exhaustive list.

Table 4-1. Facilities that Manufacture or Process Arsenic

State[a]	Number of facilities	Range of maximum amounts on site in pounds[b]	Activities and uses[c]
AL	4	1000-999999	8, 9
AR	1	No data	No data
CA	2	No data	No data
CO	1	No data	No data
FL	2	10000-99999	9
GA	3	1000-9999	2, 4, 8, 12
IL	3	10000-99999	1, 5, 9
IN	2	100000-999999	9
KY	2	1000-9999	8, 9
LA	1	No data	No data
MI	2	10-999999	9, 13
MN	1	10000-99999	8
MO	1	1000-9999	1, 2, 3, 4, 5, 7
MS	4	10000000-49999999	2, 3, 4,8, 9, 10
NC	3	1000-999999	8, 9, 10
OH	1	10000-99999	1, 6
OK	1	100-999	1, 5
PA	4	1000-99999	2, 3, 7, 8, 9
SC	2	0-999999	1, 5, 9
TN	2	10000-99999	1, 3, 8, 9
TX	4	10000-99999	1, 2, 4, 6, 8
VA	2	1000-9999	8, 9
WI	1	10000-99999	8
WV	2	1000-9999	1, 3, 8, 9, 12
WY	1	100-999	1, 6

Source: TR197 1999

[a]Post office state abbreviations used

[b]Range represents maximum 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

4.2 IMPORT/EXPORT

Since U.S. production ceased in 1985, all arsenic consumed in the United States is imported. Imports of arsenic have increased substantially since the mid-1980s, reaching 30,300 metric tons in 1998, of which 29,300 metric tons were as arsenic trioxide and 997 metric tons as the metal (USGS 1998b). The major exporting country is China, which supplied 54% of our arsenic imports in 1998, followed by Chile and Hong Kong with 27 and 8.6% of our imports, respectively.

U.S. exports of arsenic are minor with only 61 metric tons of arsenic metal being reported in 1997 and an estimated 40 metric tons in 1998 (USGS 1998b).

4.3 USE

Production of wood preservatives, primarily chrome copper arsenate (CCA), CrO_3•CuO•As_2O_5, presently accounts for more than 90% of domestic consumption of arsenic trioxide. The three principal producers of arsenical wood preservatives are Hickson Corp., Smyrna, Georgia, Chemical Specialties Inc., Harrisburg, North Carolina, and Osmose Wood Preserving, Inc., Buffalo, New York (USGS 1998a). CCA is the most widely used wood preservative in the world. Wood treated with CCA is referred to as 'pressure treated' wood (American Wood Preservers Association 2000, Page and Loar 1993). In 1997, approximately 727.8 million cubic feet (20.6 million cubic meters) of wood product were pressure treated in the United States. CCA is a water-based product that protects several commercially-available species of western lumber from decay and insect attack. It is widely used in treating utility poles, building lumber, and wood foundations. CCA comes in three types, A, B, and C that contain different proportions of chromium, copper, and arsenic oxides. Type C, the most popular type, contains CrO_3, CuO, and As_2O_5 in the proportions 47.5, 18.5, and 34.0%, respectively. The retention levels are 0.25 pounds per cubic feet (pcf) for above ground use such as fencing and decking, 0.40 pcf for lumber used in ground contact such as fence posts and deck posts, and 0.60 pcf for all weather wood foundations (Chicago Flameproof 2000; Permapost 2000). Piling used for fresh and saltwater contact should contain 0.80 and 2.5 pcf of CCA, respectively. 10,10'-Oxybisphenoxarsine (OBPA) is a leading industrial antimicrobial used primarily in the plastics industry (McEntee 1995).

Arsenic metal is used in the production of nonferrous alloys, principally lead alloys used in lead-acid batteries (USGS 1999a). Arsenic may be added to alloys used for bearing, type metal, lead ammunition,

automotive body solder. It is also added to some brasses to improve corrosion resistance (Carapella 1992). In the past, the predominant use of arsenic was in agriculture. Organic arsenicals, namely cacodylic acid, disodium methylarsenate (DSMA), monosodium methylarsenate (MSMA), and arsenic acid are still used as herbicides (Meister 1999). Cacodylic acid is also used as a silvicide and cotton defoliant. Pesticide use data from 1992 indicates that 6.0, 1.3, and 0.14 million pounds of MSMA, DSMA, and cacodylic acid, respectively, was applied to U.S. crops; the respective area treated was 3.7, 0.76, and 0.17 million acres (Gianessi and Anderson 1995d). About 99.5% of these chemicals were applied to cotton. The remainder was applied to citrus and sod.

From the mid-nineteenth century to the introduction of organic pesticides in the 1940s, inorganic arsenic compounds were the dominant pesticides available to farmers and fruit growers. Calcium arsenate was formerly used to control the boll weevil and cotton worm and used as a herbicide. Lead arsenate was used on apple and other fruit orchards as well as on potato fields. Sodium arsenite was used to control weeds on railroad right-of-ways, potato fields, and in industrial areas, as well as in baits and to debark trees. Sodium arsenate had some application in ant traps. The use of inorganic arsenic compounds in agriculture has virtually disappeared beginning around the 1960s (Azcue and Nriagu 1994; Meister 1987; Merwin et al. 1994; Sanok et al. 1995). Food uses were voluntarily cancelled in 1993 as was the use of arsenic acid as a defoliant on cotton plants; inorganic arsenic's remaining allowable uses are in ant baits and wood preservatives (EPA 1999a, 1999h). Most agricultural uses of arsenic were banned because of concerns about human health risk during production and application or accidental poisoning at the point of use (Loebenstein 1994) (see Chapter 7). Beginning about 1975, the use of arsenic as a wood preservative began to grow, and after 1980, wood preservative uses were more important than agricultural applications. By 1990, 70% of the arsenic consumed in the United States was used by the wood preservative industry and only 20% was used by the agricultural industry (Loebenstein 1994).

High purity arsenic is used in the manufacture of galium arsenide and other intermetallic compounds that are used in a variety of semiconductor applications including solar cells, light-emitting diodes, lasers, and integrated circuits (Carapella 1992; Sheehy and Jones 1993). Arsenic trioxide and arsenic acid were used as a decolorizer and fining agent in the production of bottle glass and other glassware. Arsenilic acid, (*p*-aminophenylarsonic acid) is used as a feed additive for poultry and swine, and sodium arsenite is used for cattle and sheep dips (Carapella 1992).

Arsenic compounds have a long history of use in medicine. Inorganic arsenic was used as a therapeutic agent through the mid twentieth century, primarily for the treatment of leukemia, psoriasis, and chronic

bronchial asthma; organic arsenic antibiotics were extensively used in the treatment of spirochetal and protozoal disease (National Research Council 1999). The availability of inorganic arsenicals in Western medicines ended in the 1970s, although they may still be encountered in non-Western traditional medicines. By the 1980s, the only remaining medicinal organic arsenical was melarsoprol for treatment of the meningoencephalitic stage of African trypanosomiasis. Recently, there has been renewed interest in arsenic as a therapeutic agent, namely the use of arsenic trioxide in the treatment of acute promyelocytic leukemia (APL) (Gallagher 1998; Kroemer and de Thé 1999; Miller 1998).

4.4 DISPOSAL

Wastes containing arsenic are considered hazardous wastes, and as such, their treatment, storage, and disposal are regulated by law (see Chapter 7). The main route of disposal of solid wastes containing arsenic is landfilling. EPA has promulgated rules and treatment standards for landfilling liquid arsenical wastes (EPA 1990e). Other disposal alternatives for arsenic-containing wastes include incineration and recycling. There is, however, essentially no recycling of arsenic from its principal uses in wood preservatives or agricultural chemicals (IRPTC 1990; U.S. Bureau of Mines 1990). Arsenic is not recovered from consumer end product scrap, such as treated wood. This scrap will most likely be disposed of in municipal landfills or municipal waste incinerators. No arsenic is recovered domestically from nonferrous smelting, however process water and contaminated runoff from wood treatment plants are reused and gallium arsenide scrap from semiconductor devices are processed for metal recovery (USGS 1999a).

CCA treated wood is disposed of with ordinary household trash. It should not be burned in open fires, or in stoves, residential boilers, or fire places. Treated wood from commercial or industrial applications may only be burned in commercial or industrial incinerators in accordance with state and federal regulations (Hickson 2000).

According to the Toxic Chemical Release Inventory, in 1997, an estimated 53 pounds of arsenic were released by manufacturing and processing facilities to publicly owned-treatment works (POTWs) and an estimated 989,000 pounds were transferred off-site (TRI97 1999). Arsenic is listed as a toxic substance under Section 313 of the Emergency Planning and Community Right to Know Act (EPCRA) under Title III of the Superfund Amendments and Reauthorization Act (SARA) (EPA 1995c). Disposal of wastes containing arsenic is controlled by a number of federal regulations (see Chapter 7).

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Arsenic is an element that occurs naturally in the earth's crust at an average concentration of 2–5 mg/kg, and is primarily associated with igneous and sedimentary rocks in the form of inorganic arsenic compounds (Tamaki and Frankenberger 1992). While arsenic is released to the environment from natural sources such as wind-blown dirt and volcanoes, releases from anthropogenic sources far exceed those from natural sources. Anthropogenic sources of arsenic include nonferrous metal mining and smelting, pesticide application, coal combustion, wood combustion, and waste incineration. Most anthropogenic releases of arsenic are to land or soil, primarily in the form of pesticides or solid wastes. However, substantial amounts are also released to air and water.

Arsenic released to land is predominantly inorganic and relatively immobile because it binds to soil particles. It is often primarily associated with iron and manganese oxides in soil and may therefore be released when these oxides are reduced. Soluble forms of arsenic are known to leach into shallow groundwater in areas that are geologically rich in arsenic; runoff may also enter surface water. Soil microorganism may convert inorganic arsenic to organic forms and may reduce small amounts to arsine that would volatilize into the atmosphere. In aquatic systems, inorganic arsenic occurs primarily in two oxidation states, As(V) and As(III). Both forms generally exist together although As(V) predominates under oxidizing conditions and As(III) predominates under reducing conditions. Water samples from a number of lakes and estuaries, mostly in California, show measurable concentrations of methylated arsenic (equivalent to 1–59% of total arsenic) (Anderson and Bruland 1991). The appearance of methylated species in bodies of water is correlated with algal blooms. Arsenic may undergo a variety of reactions in the environment, including oxidation-reduction reactions, ligand exchange, precipitation, and biotransformation (EPA 1979, 1984a; Pongratz 1998; Welch et al. 1988). These reactions are influenced by Eh (the oxidation-reduction potential), pH, metal sulfide and sulfide ion concentrations, iron concentration, temperature, salinity, and distribution and composition of the biota (EPA 1979; Wakao et al. 1988). Much of the arsenic will adsorb to particulate matter and sediment. Arsenic released to air exists mainly in the form of particulate matter. Arsenic released from combustion processes will generally occur as highly soluble oxides. These particles are dispersed by the wind returned to the earth in wet or dry deposition. Arsines that are released to the atmosphere as a result of microbial action are oxidized to nonvolatile species that settle back to the ground.

Because arsenic is a natural component of the earth's crust, low levels of the element are found in all environmental media. Concentrations in air in remote locations (away from human releases) range from 1 to 3 ng/m^3, while concentrations in urban areas may range from 20 to 100 ng/m^3. Concentrations in water are usually less than 10 ppb, although higher levels may occur near natural mineral deposits or anthropogenic sources. Natural levels of arsenic in soil usually range from 1 to 40 ppm, with a mean of 5 ppm, although much higher levels may occur in mining areas, at waste sites, near high geological deposits of arsenic-rich minerals, or from pesticide application. Arsenic is also found in many foods, at concentrations that usually range from 20 to 140 ppb. Concentrations may be substantially higher in certain seafoods, although much of this largely of the less harmful, organic form. Drinking water generally contains an average of 2 µg/L of arsenic, although 12% of water supplies from surface water sources in the North Central region of the country and 12% of supplies from groundwater sources in the Western region have levels exceeding 20 µg/L.

For most people, diet is the largest source of exposure, with average intakes of about 40 µg/day of total arsenic (i.e., arsenic in all of its forms). The predominant dietary source of arsenic is seafood, followed by rice/rice cereal, mushrooms, and poultry. However, most of the arsenic in seafood is of the nontoxic organic form. It is not clear what food items are the largest contributors of inorganic arsenic in the diet. U.S. dietary intake of inorganic arsenic has been estimated to range from 1 to 20 µg/day (Schoof et al. 1999a, 1999b). Intake from air, soil, and water are usually much smaller than from food, but exposure from these media may become significant in areas with naturally high levels of arsenic or with arsenic contamination. People who produce or use arsenic compounds in occupations such as nonferrous metal smelting, pesticide manufacturing or application, wood preservation, semiconductor manufacturing, or glass production may be exposed to substantially higher levels of arsenic, mainly from dusts or aerosols in air. The National Institute of Occupational Safety and Health (NIOSH) estimated that 55,000 workers were occupationally exposed to arsenic in the early 1980s. The survey did not include the mining or agricultural sectors.

Hazardous waste sites are another possible source of human exposure to arsenic. Arsenic has been identified in at least 1,014 of the 1,598 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2000). However, the number of sites evaluated for arsenic is not known. The frequency of these sites within the United States can be seen in Figure 5-1. Of these sites, 1,004 are located in the United States, 7 are located in the Commonwealth of Puerto Rico, 2 are located in the Virgin Islands (not shown), and 1 is located in Guam (not shown).

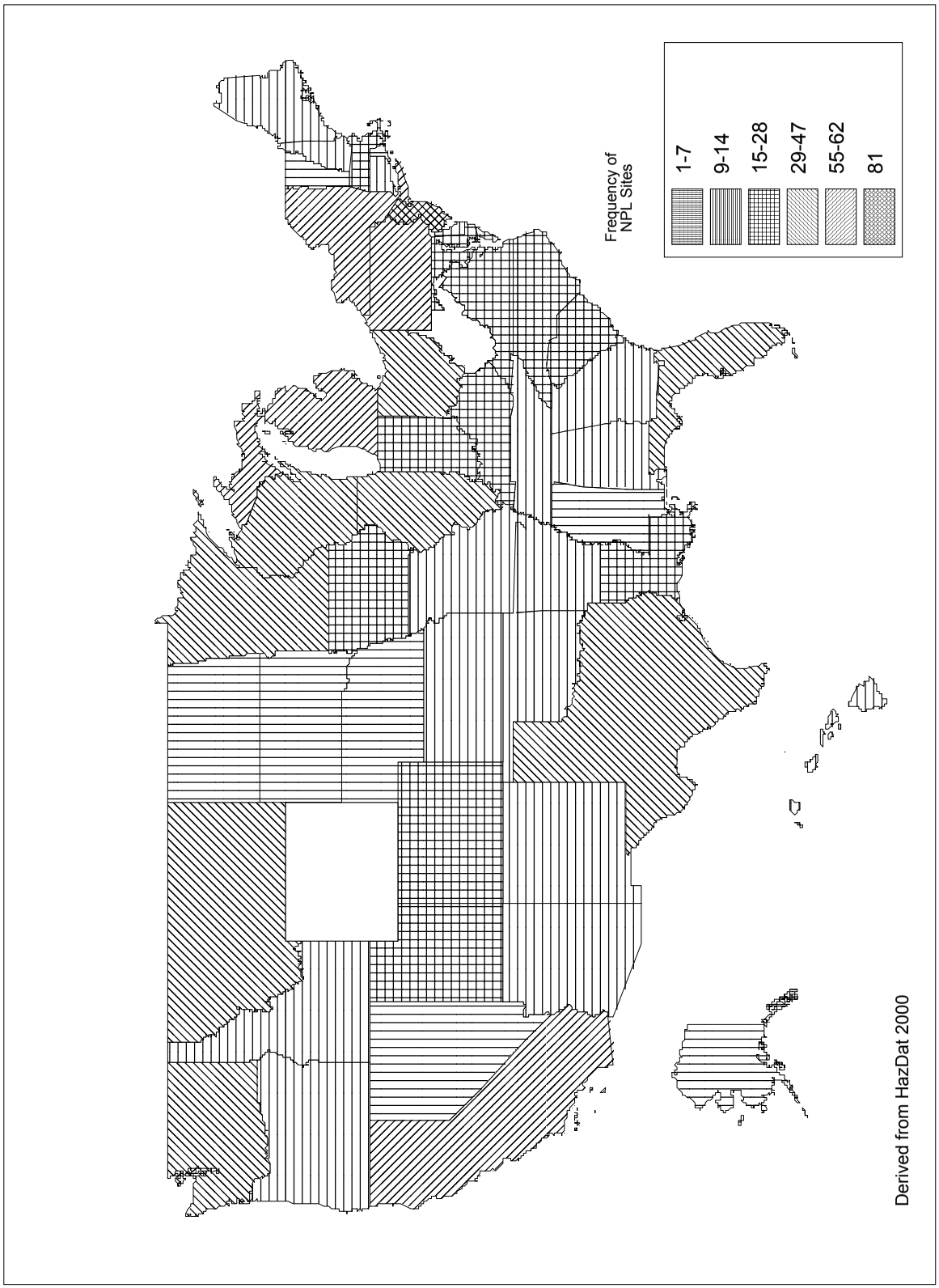


Figure 5-1. Frequency of NPL Sites with Arsenic Contamination

Exposure at waste sites may occur by a variety of pathways, including inhalation of dusts in air, ingestion of contaminated soil or water, or through the food chain. The magnitude of the exposures may be substantial, but this can only be evaluated on a site-by-site basis.

5.2 RELEASES TO THE ENVIRONMENT

According to the Toxic Chemical Release Inventory, in 1997, total releases of arsenic to the environment (including air, water, soil, and underground injection) from 52 large manufacturing or processing facilities were 60,700 pounds (TRI97 1999). Table 5-1 lists amounts released from these facilities grouped by state. In addition, 53 pounds of arsenic were released by manufacturing or processing facilities to publicly owned treatment works (POTWs) and an estimated 989,000 pounds were transferred off-site (TRI97 1999). The bulk of the releases reported to TRI were from the 'textile mill products' and 'primary metal industries' industrial sectors; releases reported from the 'lumber and wood products' industrial sector was minor even though it is the predominant user of arsenic. It should be noted that these 1997 data do not include emissions from coal combustion facilities, metal and coal mining, or pesticide spraying (EPA 1997e) which are major sources of arsenic release to the environment. The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

Arsenic has been identified in a variety of environmental media (air, surface water, leachate, groundwater, soil, and sediment) at 1,014 of the 1,598 current or former NPL hazardous waste sites (HazDat 2000). However, the number of sites evaluated for arsenic is not known. The frequency of these sites within the United States can be seen in Figure 5-1.

5.2.1 Air

Arsenic naturally occurs in soil and will be present in the atmosphere as air-borne dust. It is also emitted from volcanoes and in areas of dormant volcanism (e.g., fumaroles). Gaseous alkyl arsenic compounds may be released from soil that has been treated with inorganic arsenic compounds as a result of biogenic processes (Schroeder et al. 1987; Tamaki and Frankenberger 1992). Arsenic naturally occurs in sea water and vegetation and is released into the atmosphere in sea salt spray and forest fires. Anthropogenic sources of arsenic include nonferrous metal smelting, coal, oil and wood combustion, and municipal waste incineration. Arsenic naturally occurs in coal and oil and therefore coal- and oil-fired power plants

Table 5-1. Releases to the Environment from Facilities that Manufacture or Process Arsenic and Its Compounds

		Total of reported amounts released in pounds per year[a]						
State[b]	Number of facilities	Air[c]	Water	Land	Underground injection	Total environment[d]	POTW transfer	Off-site waste transfer
AL	4	7	2	0	0	9	No data	322
AR	1	No data	No data	No data	No data	No data	No data	No data
CA	2	No data	No data	No data	No data	No data	No data	No data
CO	1	No data	No data	No data	No data	No data	No data	No data
FL	2	4	0	0	0	4	No data	17,435
GA	3	0	0	0	0	0	No data	0
IL	3	303	93	0	0	396	No data	20,548
IN	2	0	0	502	0	502	No data	502
KY	2	0	1	0	0	1	No data	3,126
LA	1	No data	No data	No data	No data	No data	No data	No data
MI	2	10,800	0	0	0	10,800	0	444,700
MN	1	90	0	0	0	90	34	12,200
MO	1	16	2	5,860	0	5,878	No data	0
MS	4	0	0	0	0	0	0	875
NC	3	12	0	0	0	12	0	21,107
OH	1	15	0	0	0	15	No data	No data
OK	1	0	62	2	0	64	No data	No data
PA	4	129	11	0	0	140	No data	44,975

Table 5-1. Releases to the Environment from Facilities that Manufacture or Process Arsenic and Its Compounds *(continued)*

		Total of reported amounts released in pounds per year[a]						
State[b]	Number of facilities	Air[c]	Water	Land	Underground injection	Total environment[d]	POTW transfer	Off-site waste transfer
SC	2	37,771	0	0	0	37,771	10	975
TN	2	30	0	0	0	30	0	3,738
TX	4	1,352	1	3,672	0	5,025	9	412,768
VA	2	0	0	0	0	0	No data	4,200
WI	1	0	0	0	0	0	No data	280
WV	2	0	2	0	0	2	No data	1,617
WY	1	0	0	0	0	0	No data	0
Totals	**52**	**50,529**	**174**	**10,036**	**0**	**60,739**	**53**	**989,368**

Source: TRI97 1999

[a]Data in TRI are reported amounts released by each facility. No data indicates that *all* facilities reporting in a state did not submit data.
[b]Post office state abbreviations used
[c]The sum of fugitive and stack releases are included in releases to air by a given facility
[d]The sum of all releases of the chemical to air, land, and water, and underground injection wells
POTW = publicly-owned treatment works

release arsenic to the atmosphere in their emissions (Pacyna 1987). Arsenic's use in agriculture and industrial processes also contributes to its emissions. One important source of arsenic emissions is cotton ginning in which the cotton seeds are removed from the raw cotton. EPA conducted a modeling study with the Assessment System for Population Exposure Nationwide (ASPEN) in which estimates of emissions of hazardous air pollutants was used to estimate air quality (Rosenbaum et al. 1999). Using 1990 data, the total emissions of arsenic in the conterminous 48 states, excluding road dust or windblown dust from construction or agricultural tilling was estimated to be 3.0 tons/day with 90% of emissions coming from point sources, and 5% each from area and mobile sources. Nriagu and Pacyna (1988) and Pacyna et al. (1995) estimated worldwide emissions of arsenic to the atmosphere for 1983. Estimates of yearly emissions from anthropogenic sources ranged from 12,000 to 25,600 metric tons with a median value of 18,800 metric tons. Natural sources contributed 1,100–23,500 metric tons annually. Chilvers and Peterson (1987) estimated global natural and anthropogenic arsenic emissions to the atmosphere as 73,500 and 28,100 metric tons per year, respectively. Copper smelting and coal combustion accounted for 65% of anthropogenic emissions. A U.S. Bureau of Mines study on the flow of mineral commodities estimated that global emissions of arsenic from metal smelting, coal burning, and other industrial uses ranged from 24,000 to 124,000 metric tons per year compared to natural releases, mostly from volcanoes, ranging from 2,800 to 8,000 metric tons per year (Loebenstein 1994). U.S. emissions of arsenic to the atmosphere was estimated as 3,300 metric tons per year between 1979 and 1986 (Pacyna et al. 1995). There is evidence that anthropogenic emissions, at least from smelters, are lower than they had been in the early 1980s. Skeaff and Dubreuil (1997) calculated 1993 arsenic emission factors for Canadian smelters and found them to be 14, 7, and 26% for lead, copper-nickel, and zinc smelters, respectively. Significant amounts of arsenic are released in stack gases from roasting gold ores (Environment Canada 1993). It is likely that air releases of arsenic decreased during the 1980s due to regulations on industrial emissions (EPA 1986f), improved control technology for coal-burning facilities, and the decreased use of arsenical pesticides.

Pirrone and Keeler (1996) compared trends of trace element emissions from major anthropogenic sources in the Great Lakes region with ambient concentrations observed in urban areas of the region. They found that arsenic emissions increased about 2.8% per year from 1982 to 1988 and then decreased steadily by about 1.4% per year to 1993. Coal combustion in electric utilities and in residential, commercial, and industrial facilities was an important source of arsenic in the region, accounting for about 69% of the total emissions. Iron-steel manufacturing accounted for about 13% of the region wide arsenic emissions and nonferrous metals production for 17%.

Inorganic species, most commonly trivalent arsenic, is the dominant form of arsenic in the air over emission areas; methylated forms of arsenic are probably of minor significance. Arsenic-containing air samples of smelter or coal-fired power plant origin consist largely of trivalent arsenic in both vapor and particulate form (Pacyna 1987). Oxides are the primary species evolved from fossil fuel and industrial processes. Additionally, arsenic trisulfide has also been reported from coal combustion, organic arsines from oil combustion, and arsenic trichloride from refuse incineration.

According to the Toxic Chemical Release Inventory, in 1997, the estimated releases of arsenic of 50,500 pounds to the air from 52 large processing facilities accounted for 83% of total environmental releases (TRI97 1999). Table 5-1 lists amounts of arsenic and its compounds released to air from these facilities grouped by state. It should be noted that these 1997 data do not include emissions from coal combustion facilities, metal and coal mining, or pesticide spraying (EPA 1997e) which are major sources of arsenic release to air. The TRI data should be used with caution, however, since only certain types of facilities are required to report. This is not an exhaustive list.

Arsenic has been identified in 53 air samples collected from 1,014 current or former NPL hazardous waste sites where it was detected in some environmental media (HazDat 2000).

5.2.2 Water

Arsenic may be released to water from the natural weathering of soil, rocks, and in areas of vulcanism. Arsenic may also leach from soil and minerals into groundwater. Anthropogenic sources of arsenic releases to water include mining, nonferrous metals, especially copper, smelting, waste water, dumping of sewage sludge, coal burning power plants, manufacturing processes, urban runoff, and atmospheric deposition (Nriagu and Pacyna 1988; Pacyna et al. 1995). A contributory part of mining and coal burning power plants is leaching from abandoned mine tailing and fly ash waste piles. Significant amounts of arsenic are released in liquid effluents from gold-milling operations using cyanide (Environment Canada 1993). Nriagu and Pacyna (1988) and Pacyna et al. (1995) estimated global anthropogenic inputs of arsenic into rivers, lakes, and oceans for 1983. Annual estimated inputs ranged from 11,600 to 70,300 metric tons with a median value of 41,800 metric tons.

According to the Toxic Chemical Release Inventory, in 1997, the reported releases of 170 pounds of arsenic and its compounds to water from 52 large processing facilities accounted for 0.29% of the total environmental releases (TRI97 1999). An additional 53 pounds of arsenic were released indirectly to

POTWs and some of this volume ultimately may have been released to surface waters. Table 5-1 lists amounts of arsenic released to water and POTWs from these facilities grouped by state. The TRI data should be used with caution, however, since only certain types of facilities are required to report. This is not an exhaustive list.

Leaching of arsenic from soil, landfills, or slag deposits is a source of arsenic in groundwater (Francis and White 1987; Wadge and Hutton 1987). The arsenic in soil may be naturally-occurring or a result of the application of arsenic-containing pesticides or sludge. Wood treated with chromated copper arsenate is used widely in piers, piling and bulkheads and arsenic readily leaches from the treated wood (Sanders et al. 1994). Arsenic has been identified in 1,147 groundwater and 370 surface water samples collected from 1,014 NPL hazardous waste sites, where it was detected in some environmental media (HazDat 2000).

Arsenic was detected in 58% of samples of urban storm water runoff from 8 of 15 cities surveyed in the National Urban Runoff Program at concentrations ranging from 1 to 50.5 ppb (Cole et al. 1984).

5.2.3 Soil

The soil receives arsenic from a variety of anthropogenic sources, including ash residue from power plants, smelting operations, mining wastes, and municipal, commercial, and industrial waste. Ash from power plants is often incorporated into cement and other materials that are used for roads and construction. Arsenic may be released from such material into soil. Similarly, wood treated with chrome copper arsenate (CCA) used in foundations or posts could potentially release arsenic into the surrounding soil. Arsenic may also be released on land through the application of pesticides and fertilizer. Senesi et al. (1999) reported the range of arsenic in 32 fertilizers as 2.2–322 ng/g. Land application of sewage sludge is another source of arsenic in soil. Arsenic was detected in sewage sludge samples from 23 cities at concentrations of 0.3–53 ppm (Mumma et al. 1984). Nriagu and Pacyna (1988) and Pacyna et al. (1995) estimated global anthropogenic inputs of arsenic into soil for 1983. Excluding mine tailings and smelter slag, annual estimated inputs ranged from 52,000 to 112,000 metric tons with a median value of 82,000 metric tons. Mine tailings and smelter slag was estimated to add an additional 7,200–11,000 and 4,500–9,000 metric tons, respectively. Old abandoned mine tailings undoubtably contribute still more.

According to the Toxic Chemical Release Inventory, in 1997, reported releases of 10,000 pounds of arsenic to soil from 52 large processing facilities accounted for 17% of total environmental releases of

arsenic (TRI97 1999). No arsenic was released via underground injection in 1997. Table 5-1 lists amounts of arsenic released on land from these facilities grouped by state. The TRI data should be used with caution, however, since only certain types of facilities are required to report. This is not an exhaustive list.

Arsenic has been identified in 972 soil and 492 sediment samples collected from 1,014 NPL hazardous waste sites, where it was detected in some environmental media (HazDat 2000).

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

Arsenic in soil may be transported by wind or in runoff or may leach into the subsurface soil. However, because many arsenic compounds tend to partition to soil or sediment under oxidizing conditions, leaching usually does not transport arsenic to any great depth (EPA 1982c; Moore et al. 1988; Pantsar-Kallio and Manninen 1997; Welch et al. 1988). Arsenic is largely immobile in agricultural soils; therefore, it tends to concentrate and remain in upper soil layers indefinitely. Downward migration has been shown to be greater in a sandy soil than in a clay loam (Sanok et al. 1995). Arsenic from lead arsenate that was used for pest control did not migrate downward below 20 cm in one fruit orchard; in another orchard, 15 years after sludge amendments and deep plowing, essentially all arsenic residues remained in the upper 40 cm (Merwin et al. 1994). Leaching of arsenic in polluted wetland soil was low; leaching was correlated with the amount of dissolved organic matter in the soil (Kalbitz and Wennrich 1998). The effect of soil characteristics, namely pH, organic matter content, clay content, iron oxide content, aluminum oxide content, and cation exchange capacity (CEC), on the adsorption of various metals to 20 Dutch surface soils was assessed by regression analysis (Janssen et al. 1997). The most influential parameter affecting arsenic, and the only one of any significance, was the iron content of the soil. Arsenic which is adsorbed to iron and manganese oxides may be released under reducing conditions which may occur in sediment or flooding conditions (LaForce et al. 1998; McGeehan 1996; Mok and Wai 1994). In addition to reductive dissolution, when nutrient levels are adequate, microbial action can also result in dissolution. Interestingly, drying of the previously flooded soil increases arsenic adsorption, possibly due to alterations in iron mineralogy (McGeehan et al. 1998).

Darland and Inskeep (1997) conducted a study to determine the effects of pH and phosphate competition on the transport of arsenate (AsO_4) through saturated columns filled with a sand containing free iron

oxides. At pH 4.5 and 6.5, AsO_4 transport was strongly retarded, while at pH 8.5 it was rapid. The enhanced transport of AsO_4 at pH 8 is consistent with the pH dependence of surface complexation reactions describing AsO_4 sorption by metal oxide minerals that can be categorized as a ligand exchange mechanism. Phosphate was shown to compete effectively with AsO_4 for adsorption sites on the sand, but the competition was not sufficient to desorb all of the AsO_4 in batch column experiments, even when the applied phosphate exceeded the column adsorption capacity by a factor of two. The researchers concluded that AsO_4 desorption kinetics may play an important role in the transport of AsO_4 through porous media.

Smith et al. (1999) investigated the sorption properties of both As(V) and As(III) in 10 Australian soils of widely different chemistry and mineralogy at commonly found arsenic levels. Adsorption of both arsenate and arsenite was rapid (1 hour). The amount of As(V) sorbed varied widely (1.7–62.0 L/kg); soils with lower amounts of oxidic material adsorbed much less arsenic than those with higher amounts of these minerals. Arsenate sorption was highly correlated with the iron oxide content of the soil and this factor probably accounts for much of the variation in soil adsorptivity. Considerable leaching of arsenic occurred at a cattle dip site that contained similar soil. Arsenite adsorption, which was investigated in four of the Australian soils, was sorbed to a lesser extent than was arsenate. This was attributed to soil minerology and the species of As(V) and As(III) present in solution; at pH 5–7, the dominant species are $H_2AsO_4^-$ and $HAsO_4^{2-}$ (As(V)) and neutral H_3AsO_3 (As(III)). For soils containing low amounts of oxidic minerals, pH had little effect on As(V) sorption, while for oxidic soils, a decrease in sorption was evident as the pH increased. In contrast, As(III) sorption increased with increasing pH.

The practice of liming to remediate contaminated soils and mine tailings has the potential to mobilize arsenic. Experiments performed by Jones et al. (1997) indicate that the increased mobility appears to be consistent with the pH dependence of sorption reactions of arsenic on iron oxide minerals rather than dissolution-precipitation reactions involving arsenic. They recommend that remediation of acidic mine tailings or other arsenic-contaminated soils be carefully evaluated with respect to potential arsenic mobilization, especially at contaminated sites hydraulically connected to surface or groundwaters.

Transport and partitioning of arsenic in water depends upon the chemical form (oxidation state and counter ion) of the arsenic and on interactions with other materials present. Soluble forms move with the water, and may be carried long distances through rivers (EPA 1979). However, arsenic may be adsorbed from water onto sediments or soils, especially clays, iron oxides, aluminum hydroxides, manganese compounds, and organic material (EPA 1979, 1982c; Welch et al. 1988). Under oxidizing and mildly

reducing conditions, groundwater arsenic concentrations are usually controlled by adsorption rather than by mineral precipitation. The extent of arsenic adsorption under equilibrium conditions is characterized by the distribution coefficient, K_d, which measures the equilibrium partitioning ratio of adsorbed to dissolved contaminant. The value of K_d depends strongly upon the pH of the water, the arsenic oxidation state, and the temperature. In acidic and neutral waters, As(V) is extensively adsorbed, while As(III) is relatively weakly adsorbed. This is because As(III), which exists as H_3AsO_3 (pK_a=9.23, 12.13, 13.4), is less strongly adsorbed on mineral surfaces than the oxyanions of H_3AsO_4 (pK_a=2.22, 6.98, 11.53) (NRC 1999). In waters with a high pH, K_d values are considerably lower for both oxidation states (Mariner et al. 1996). Sediment-bound arsenic may be released back into the water by chemical or biological interconversions of arsenic species (see Section 5.3.2).

Arsenic enters rivers from where mining operations occurred and are transported downstream, moving from water and sediment into biofilm (attached algae, bacterial, and associated fine detrital material), and then into invertebrates and fish. The source of arsenic in the water column may be resuspended sediment. While arsenic bioaccumulates in animals, it does not appear to biomagnify between tropic levels (Eisler 1994; Farag et al. 1998).

Most anthropogenic arsenic emitted to the atmosphere arise from high temperature processes from tall stacks and occur as fine particles with a mass median diameter of about 1 µm (Coles et al. 1979; Pacyna 1987). These particles are transported by wind and air currents until they are returned to earth by wet or dry deposition. Their residence time in the atmosphere is about 7–9 days, in which time the particles may be transported thousands of kilometers (EPA 1982b; Pacyna 1987). Long range transport was evident in analyzing deposition of arsenic in countries like Norway; there was no indication that the marine environment contributed significantly to the deposition (Steinnes et al. 1992). Atmospheric fallout can be a significant source of arsenic in coastal and inland waters near industrial areas. Scudlark et al. (1994) determined the average wet depositional flux of arsenic as 49 µg As/m^2/year for 2 sites in Chesapeake Bay, Maryland from June 1990 to July 1991. They found a high degree of spatial and temporal variability. The elemental fluxes derived predominantly from anthropogenic sources. Golomb et al. (1997) report average total (wet + dry) deposition rates to Massachusetts Bay of 132 µg/m^2/year of which 21 µg/m^2/year was wet deposition during the period September 15, 1992 to September 16, 1993. Hoff et al. (1996) estimated the following arsenic loadings into the Great Lakes for 1994 (Lake, wet deposition, dry deposition): Superior, 11,000 kg/year, 3,600 kg/year; Michigan, 5,000 kg/year, 1,800 kg/year; Erie, 5,500 kg/year, 1,800 kg/year; and Ontario, 3,000 kg/year, 580 kg/year.

Terrestrial plants may accumulate arsenic by root uptake from the soil or by absorption of airborne arsenic deposited on the leaves, and certain species may accumulate substantial levels (EPA 1982b). Yet even when grown on highly polluted soil or soil naturally high in arsenic, the arsenic level taken up by the plants is comparatively low (Gebel et al. 1998b; Pitten et al. 1999). Kale, lettuce, carrots, and potatoes were grown in experimental plots surrounding a wood preservation factory where waste wood was incinerated to investigate the amount and pathways for arsenic uptake by plants (Larsen et al. 1992). On incineration, the arsenate in the wood preservative was partially converted to arsenite; the arsenic emitted from the stack was primarily particle bound. Elevated levels of inorganic arsenic were found in the test plants and in the soil around the factory. Statistical analyses revealed that the dominating pathway for transport of arsenic from the factory to the leafy vegetables (kale) was by direct atmospheric deposition, while arsenic in the root crops (potatoes and carrots) was a result of both soil uptake and atmospheric deposition. Arsenic accumulation by plants is affected by arsenic speciation. Uptake of four arsenic species (arsenite, arsenate, methylarsonic acid, and dimethylarsinic acid) by turnip grown under soilless culture conditions showed that while uptake increased with increasing arsenic concentration in the nutrient, the organic arsenicals showed higher upward translocation than the inorganic arsenical (Carbonell-Battachina et al. 1999). The total amount of arsenic taken up by the turnip plants followed the trend monomethylarsenate (MMA)<dimethylarsinic acid (DMA)<arsenite<arsenate. Terrestrial plants growing on land bordering arsenic-contaminated waters show relatively little arsenic content even though the sediments have arsenic concentrations as high as 200 µg/g (Tamaki and Frankenberger 1992).

Bioconcentration of arsenic occurs in aquatic organisms, primarily in algae and lower invertebrates. Both bottom-feeding and predatory fish can accumulate contaminants found in water. Bottom-feeders are readily exposed to the greater quantities of metals that accumulate in sediments. Predators may bioaccumulate metals from the surrounding water or from feeding on other fish, including bottom-feeders, which can result in the biomagnification of the metals in their tissues. An extensive study of the factors affecting bioaccumulation of arsenic in two streams in western Maryland in 1997–1998 found found no evidence of biomagnification since arsenic concentrations in organisms tend to decrease with increasing tropic level (Mason et al. 2000). Arsenic is mainly accumulated in the exoskeleton of invertebrates and in the livers of fish. No difference in were found in the arsenic levels in different species of fish, which included herbivorous, insectivorus, and carnivorus species. The major bioaccumulation transfer is between water and algae, at the base of the food chain and this has a strong impact on the concentration in fish. National Contaminant Biomonitoring data produced by the Fish and Wildlife Service were used to test whether differences exist between bottom-feeders and predators in tissue levels of metals and other contaminants. No differences were found for arsenic (Kidwell et al.

1995). Bioconcentration factors (BCFs) measured in freshwater invertebrates and fish for several arsenic compounds ranged from 0 to 17, but a BCF of 350 was observed in marine oysters (EPA 1980a). The BCFs of bryophytes, invertebrates, and fish (livers) in Swedish lakes and brooks impacted by smelter emissions were 8,700, 1,900–2,200, and 200–800, respectively (Lither et al. 1995). In a study conducted at the Times Beach Confined Disposal Facility in Buffalo, New York, arsenic concentrations in tissue from zebra mussels exposed for 34 days were significantly higher than water column concentrations (Roper et al. 1996). Barnacles growing on chromated-copper-arsenate-treated wood docks accumulated arsenic (Weis et al. 1993). The highest concentrations of arsenic was found on the most recently treated wood. Biomagnification in aquatic food chains does not appear to be significant (EPA 1979, 1982b, 1983e; Mason et al. 2000), although some fish and invertebrates contain high levels of arsenic compounds.

5.3.2 Transformation and Degradation

5.3.2.1 Air

Arsenic is released into the atmosphere primarily as arsenic trioxide or, less frequently, in one of several volatile organic compounds, mainly arsines (EPA 1982b). Trivalent arsenic and methyl arsines in the atmosphere undergo oxidation to the pentavalent state (EPA 1984a), and arsenic in the atmosphere is usually a mixture of the trivalent and pentavalent forms (EPA 1984a; Scudlark and Church 1988). Photolysis is not considered an important fate process for arsenic compounds (EPA 1979).

5.3.2.2 Water

Arsenic in water can undergo a complex series of transformations, including oxidation-reduction reactions, ligand exchange, precipitation, and biotransformation (EPA 1979, 1984a; Sanders et al. 1994; Welch et al. 1988). Rate constants for these various reactions are not readily available, but the factors most strongly influencing fate processes in water include Eh (the oxidation-reduction potential), pH, metal sulfide and sulfide ion concentrations, iron concentrations, temperature, salinity, and distribution and composition of the biota (EPA 1979; Wakao et al. 1988). No formation of arsine gas from marine environments has been reported (Tamaki and Frankenberger 1992).

Inorganic species of arsenic are predominant in the aquatic environment, occurring mainly as As(V) in oxidizing environments such as surface water and As(III) under reducing conditions such as may occur in

groundwater containing high levels of arsenic. However, the reduction of arsenate to arsenite is slow, so arsenate can be found in reducing environments. Conversely, the oxidation of arsenite in oxidizing environments is moderately slow (half-life 0.4–7 days in coastal systems) and therefore arsenite can be found in oxidizing environments (Mariner et al. 1996; Sanders et al. 1994). The main organic species in freshwater are methylarsonic acid and dimethylarsinic acid (Eisler 1994). In the pH range of natural waters, the predominant aqueous arsenate species are $H_2AsO_4^-$ and $HAsO_4^{2-}$. The predominant arsenite species is H_3AsO_3 (Aurillo et al. 1994; EPA 1982c). Aquatic microorganisms may reduce the arsenate to arsenite and the methylated arsenicals MMA and DMA (Aurillo et al. 1994; Benson 1989; Braman and Foreback 1973; Edmonds and Francesconi 1987; Gao and Burau 1997; Sanders et al. 1994). Methylated species are also produced by the biogenic reduction of more complex organoarsenic compounds like arsenocholine or arsenobetaine. Water samples from a number of lakes and estuaries, mostly in California, show measurable concentrations of methylated arsenic (equivalent to 1–59% of total arsenic) (Anderson and Bruland 1991). Within the oxic photic zone, arsenate and dimethyl arsenic acid (DMA) were the dominant species. A seasonal study of one lake demonstrated that DMA was the dominant form of arsenic in surface waters during late summer and fall. Methylated species declined and arsenate species increased when the lake turned over in late fall. Mono Lake, a highly alkaline body of water, and four rivers did not have measurable concentrations of methylated arsenic. It was hypothesized that the reason why methylated forms were not detected in Mono Lake was that the extremely high inorganic arsenic concentrations in the lake, 230,000 nM, could overwhelm the analysis of small amounts of organic forms. Other possibilities are that the high alkalinity or very high phosphate levels in the water, 260 µM, are not conducive to biogenic methylation. At typical freshwater concentrations, the barium ion, in forming barium arsenate, is the most likely metal capable of holding total dissolved metals to low concentrations (EPA 1979). Other metals considered were calcium, iron, and chromium. Both reduction and methylation of As(V) may lead to increased mobilization of arsenic, since As(III), dimethylarsinates, and monomethylarsonates are much less particle-reactive than As(V) (Aurillo et al. 1994). In the estuarial Patuxet River, Maryland, arsenate concentrations peaked during the summer, at 1.0 µg/L in 1988–1989 (Sanders et al. 1994). In contrast winter to spring levels were around 0.1 µg/L. Arsenite concentrations was irregularly present at low levels during the year. Peaks of DMA occurred at various times, particularly in the winter and late spring and appeared to be linked with algal blooms. The DMA peak declined over several months that was followed by a rise in MMA. The MMA was thought to be occurring as a degradation product of DMA. A similar seasonal pattern of arsenic speciation was observed in Chesapeake Bay. Arsenite and methylation took place during the warmer months leading to changes down the main stem of the bay; arsensite production dominated the upper reaches of the bay and methylated species dominated the more saline lower reaches. In coastal waters, reduced and methylated

species are present in lower concentrations, around 10–20% of total arsenic. Arsenate often predominates in groundwater, but arsenite may be an important component, depending upon the characteristics of the water and surrounding geology (Robertson 1989; Welch et al. 1988).

5.3.2.3 Soil

The arsenic cycle in soils is complex, with many biotic and abiotic processes controlling its overall fate and environmental impact. Arsenic in soil exists in various oxidation states and chemical species, depending upon soil pH and redox potential. Arsenate [(As(V)] and arsenite [As(III)] exist as oxyanions in oxidized systems, while metallic arsenic [As(0)], arsine [As(-III)] and methylated forms of arsenic are thermodynamically stable in reduced systems, such as swamp and bogs. The arsenate and arsenite oxyanions have various degrees of protonation depending upon pH (EPA 1982b; McGeehan 1996). As(V) predominates in aerobic soils, and As(III) predominates in slightly reduced soils (e.g., temporarily flooded) (EPA 1982b). Transformations between the various oxidation states and species of arsenic occur as a result of biotic or abiotic processes (Bhumbla and Keefer 1994). Arsenicals applied to soils may be methylated by microorganisms to arsines which are lost through volatilization and organic forms may be mineralized to inorganic forms (Gao and Burau 1997). Cumulative arsine evolution from arsenical-amended soil followed the order: cacadilyic acid>MMA>As(III)=As(V). Arsenites are of greater environmental concern than arsenates because of their greater toxicity and higher mobility in soil (McGeehan 1996). Sulfidic mining wastes may contain arsenopyrite that oxidizes to forms arsinic acid, a highly mobile form of arsenic under acid conditions. Organoarsenical pesticides (e.g., MMA, DMA) applied to soil are metabolized by soil bacteria to alkylarsines, arsenate, and MMA. They may also be mineralized to inorganic arsenic (Gao and Burau 1997; Hood 1985). The half-life of DMA in soil is about 20 days (Hood 1985).

A sequential fractionation scheme was used to assess the chemical nature, and thus the potential bioavailability of arsenic at cattle dip sites in Australia where sodium arsenite was used extensively in cattle dips from the turn of the century until the early 1950s (McLaren et al. 1998). Most sites contained substantial amounts, 13% on the average, of arsenic in the two most labile fractions indicating a high potential for bioaccessibility and leaching. The bulk of the arsenic appeared to be associated with amorphous iron and aluminum minerals in soil. Similarly, arsenic in soil and mine waste in the Tamar Valley in England was found to be concentrated in a fraction associated with iron and organic-iron (Kavanagh et al. 1997). Laboratory studies were performed to assess the phase partitioning of trace metals to sediment from the Coeur d'Alene River, a mining area of Idaho, and the release of metals under

simulated minor and major flooding events (LaForce et al. 1998). Arsenic was primarily associated with the iron and manganese oxides as seen by its large release when these oxides were reduced. Arsenic levels were comparatively low in the organic fraction and remaining residual fraction and negligible in the extractible fractions.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to arsenic depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. In reviewing data on arsenic 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.

5.4.1 Air

Arsenic in ambient air is usually a mixture of particulate arsenite and arsenate; organic species of negligible importance except in areas of substantial methylated arsenic pesticide application or biotic activity (EPA 1984a). Mean levels in ambient air in the United States have been reported to range from <1 to 3 ng/m^3 in remote areas and from 20 to 30 ng/m^3 in urban areas (Davidson et al. 1985; EPA 1982c; IARC 1980; NAS 1977a). EPA conducted a modeling study with the Assessment System for Population Exposure Nationwide (ASPEN) in which estimates of emissions of hazardous air pollutants were used to estimate ambient concentrations (Rosenbaum et al. 1999). Using 1990 data to estimate total emissions of arsenic in the conterminous 48 states, excluding road dust or windblown dust from construction or agricultural tilling, the 25th percentile, median, and 75th percentile arsenic concentration was estimated to be 9, 20, and 30 ng/m^3, respectively. Maps with estimated county median ambient air concentrations of arsenic are available on the internet at http://www.epa.gov/ttn/uatw/nata. Schroeder et al. (1987) listed ranges of arsenic concentrations in air of 0.007–1.9, 1.0–28, and 2–2,320 ng/m^3 in remote, rural, and urban areas, respectively. The average annual arsenic concentration in air at Nahant, MA, just north of Boston, between September 1992 and September 1993, was 1.2 ng/m^3; 75% of the arsenic was associated with fine (<2.5 μm) particles. The long-term means of the ambient concentrations of arsenic measured in urban areas of the Great Lakes region from 1982 to 1993 ranged from 4.2 to 9.6 ng/m^3 (Pirrone and Keeler 1996). Large cities generally have higher arsenic air concentrations than smaller ones due to emissions from coal-fired power plants (IARC 1980), but maximum 24-hour concentrations generally are less than 100 ng/m^3 (EPA 1984a). In the spring of 1990, aerosols and cloud water that were sampled by aircraft at an altitude of 1.2–3 km above Midwestern United States had a mean mixed layer arsenic

concentration of 1.6±0.9 ng/m^3 (Burkhard et al. 1994a). The mean arsenic concentration at a site 400 km to the northwest, directly downwind on most days, was 1.0±0.5 ng/m^3

Arsenic was monitored at an application site in the San Joaquin Valley, California and at four sites in nearby communities in 1987 where sodium arsenite was used as a fungicide on tokay grapes (Baker et al. 1996). The maximum arsenic concentration measured 15–20 meters from the edge of the field was 260 ng/m^3. The maximum arsenic concentration at four community sites in the area was 76 ng/m^3. The concen-tration at an urban background site was 3 ng/m^3 (Baker et al. 1996). Sodium arsenite is not longer registered in California (Baker et al. 1996). The highest arsenic levels detected in the atmosphere were near nonferrous metal smelters, with reported concentrations up to 2,500 ng/m^3 (IARC 1980; NAS 1977a; Schroeder et al. 1987).

Arsenic air concentrations measured in several indoor public places (e.g., cafeteria, coffee house, music club, Amtrak train, and several restaurants) with environmental tobacco smoke (ETS) ranged from <0.1 to 1 ng/m^3, with a mean of 0.4±0.3 ng/m^3. Sites that were ETS-free (university office and library) had arsenic concentrations <0.13 ng/m^3 (Landsberger and Wu 1995).

5.4.2 Water

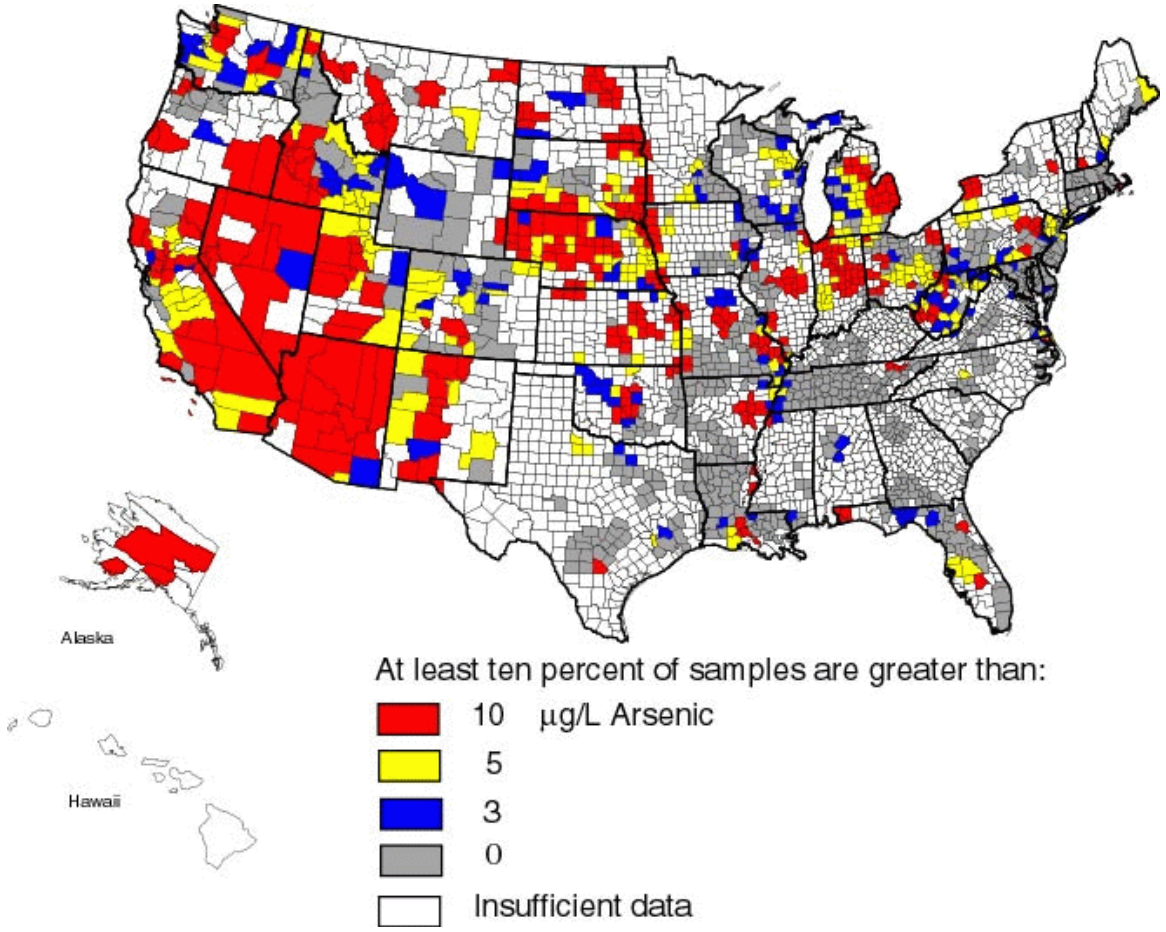
Arsenic is widely distributed in surface water, groundwater, and finished drinking water in the United States. Surveys of arsenic concentrations in rivers and lakes indicate that most values are below 10 µg/L, although individual samples may range up to 1,000 µg/L (NAS 1977b; Page 1981; Smith et al. 1987; Welch et al. 1988). A survey of 293 stations in two nationwide sampling networks on major U.S. rivers found median arsenic levels to be 1 µg/L; the 75th percentile level was 3 µg/L (Smith et al. 1987). The median arsenic concentration for surface water samples recorded in the STORET database was 3 µg/L (EPA 1982b). Twelve of the 13 surface water supplies in the National Contaminant Occurrence Database (NCOD) contained arsenic; the mean arsenic concentration in these public water systems was 0.650±0.480 µg/L (EPA 2000). All data on public water systems in the NCOD have been submitted by states to the Safe Drinking Water Information System. Two streams in western Maryland that were the focus of a major bioaccumulation study in 1997–1998 had arsenic concentrations of 0.370±0.200 and 0.670±0.460 µg/L (Mason et al. 2000). Surface water will be impacted by runoff from polluted sites. In Whitewood Creek, South Dakota, where as much as 100 million tons of mining and milling waste derived from gold mining activities were discharged between 1876 and 1977, mean sediment arsenic levels were 1,920 µg/g; dissolved-phase and particulate phase arsenic levels in the creek water ranged from 20 to

80 and 20 to 8,000 µg/L, respectively (Goddard 1987). River water sampled next to mine dumps during the rainy season in Zimbabwe had an arsenic concentration of 25 µg/L (Jonnalagadda and Nenzou 1996).

Recent data on total arsenic in surface water from a number of seas and oceans show levels of <1 µg/L, except in the Antarctic Ocean and Southwest Pacific Oceans where the levels are 1.1 and 1.2 µg/L, respectively. Levels in coastal waters and estuaries are generally somewhat higher, in the range of 1–3 µg/L. However estuarine water in Salinas, California had arsenic levels of 7.42 µg/L (Francesconi et al. 1994). The dissolved arsenic concentration in water at 40 sites in the Indian River Lagoon System in Florida ranged from 0.35 to 1.6 µg/L with a mean of 0.89±0.34 µg/L (Trocine and Trefry 1996). Thermal waters generally have arsenic levels of 20–3,800 µg/L, although levels as high as 276,000 µg/L have been recorded (Eisler 1994).

Arsenic levels in groundwater average about 1–2 µg/L, except in some western states with volcanic rock and sulfidic mineral deposits high in arsenic, where arsenic levels up to 3,400 µg/L have been observed (IARC 1980; Page 1981; Robertson 1989; Welch et al. 1988). In western mining areas, groundwater arsenic concentrations up to 48,000 µg/L have been reported (Welch et al. 1988). The U.S. Geological Survey mapped concentrations of arsenic in approximately 30,000 groundwater samples collected between 1973 and 1997 (USGS 2000). The counties in which at least 10% of wells exceed various levels is shown in Figure 5-2. All 20 of the groundwater sources in the NCOD contained arsenic; the mean arsenic concentration in these public water systems was 0.327±0.443 µg/L (EPA 2000). All data on public water systems in the NCOD have been submitted by states to the Safe Drinking Water Information System. Most arsenic in natural waters is a mixture of arsenate and arsenite, with arsenate usually predominating (Braman and Foreback 1973; EPA 1982c, 1984a). Methylated forms have also been detected in both surface and groundwater, at levels ranging from 0.01 to 7.4 µg/L (Braman and Foreback 1973; Hood 1985), with most values below 0.3 µg/L (Hood 1985). In a survey of shallow groundwater quality in the alluvial aquifer beneath a major urban center, Denver, Colorado, arsenic levels in the 30 randomly-chosen wells sampled had median levels of <1 µg/L; the maximum level was 33 µg/L (Bruce and McMahon 1996). Arsenic levels in groundwater sometimes exceeded the EPA maximum contaminant level (MCL) of 50 µg/L in the Willamette Valley, Oregon and a nine-county region of southeastern Michigan (USGS 1999b, 1999c). Areas of the world such as Bangladesh have shallow aquifers composed of arsenic-containing sediment. Arsenic is released into groundwater when the oxygen levels in the aquifer become low and iron and manganese oxyhydroxides that bind arsenic dissolve and release it into the surrounding water that the population relies on for drinking. In four

Figure 5-2. Counties in Which at Least 10% of Wells Exceed Different Arsenic Levels



Source: USGS 2000. http://co.water.usgs.gov/trace/pubs/arsenic_fig1.html

villages that were targeted for a recent study, arsenic concentrations in drinking water ranged from 10 to 2,040 µg/L (Tondel et al. 1999).

Arsenic has also been detected in rain water at average concentrations of 0.2–0.5 µg/L (Welch et al. 1988). This range is consistent with that found in a 1997–1998 study in western Maryland, which was the focus of a major bioaccumulation study (Mason et al. 2000). Arsenic levels in wet deposition in the watershed as well as throughfall into the two streams were 0.345±0.392, 0.400±0.400, and 0.330±0.250 µg/L, respectively.

Drinking water is one of the most important sources of arsenic exposure. Surveys of drinking water in the United States have found that more than 99% of public water supplies have arsenic concentrations below the EPA MCL of 50 µg/L (EPA 1984a). In an EPA study of tap water from 3,834 U.S. residences, the average value was 2.4 µg/L (EPA 1982c). Anticipated action to lower the 1974 MCL have resulted in studies to ascertain how different standards would affect compliance. One such survey sponsored by the Water Industry Technical Action Fund was the National Arsenic Occurrence Survey (NAOS). NAOS was based on a representational survey of public water systems defined by source type, system size, and geographical location. Additionally, it included a natural occurrence factor, a stratifying variable that could qualitatively describe the likelihood of arsenic occurrence in the supply. To predict finished water arsenic concentrations, data on the water treatment options, efficiency, and frequency of use were factored in. The results of the NAOS is presented in Table 5-2. The NAOS results are in general agreement with two older and more limited national surveys, EPA's National Inorganics and Radionuclides Survey (NIRS) and the Metropolitan Water District of Southern California Survey (MWDSC). The percentage of water systems that would be out of compliance is estimated to be 1.7, 3.6, 9.3, and 20.7% for arsenic MCLs of 20, 10, 5, and 2 µg/L, respectively. The north central region and the western region of the United States have the highest arsenic levels in surface water and groundwater sources, respectively. To quantify arsenic exposure for domestic well users in New Hampshire, 992 randomly selected household water samples were analyzed and the results for domestic well users compared with those those for users of municipal water supplies (Peters et al. 1999). The concentrations ranged from <0.0003 to 180 µg/L with water from domestic wells containing significantly more arsenic than water from municipal supplies; the median concentration of the former was about 0.5 µg/L and the latter 0.2 µg/L. At the present 50 µg/L MCL, none of the municipal supplies exceeded the standard and 2% of the domestic well users are out of compliance. Approximately 2% of the municipal water users have water with arsenic levels exceeding 10 µg/L compared with 13% of domestic wells. At the lowest MCL being considered, 2 µg/L, 25% of domestic wells would exceed the limit compared with about 5%

Table 5-2. Regional Occurrence of Arsenic in U.S. Water Sources and Finished Drinking Water[a]

	Arsenic Concentration - µg/L			
Geographical Region	<1	1–5	5–20	>20
Occurrence in U.S. surface water sources				
Region 1. New England	50	50	0	0
Region 2. Mid-Atlantic	84	12	4	0
Region 3. South East	93	7	0	0
Region 4. Midwest	24	76	0	0
Region 5. South Central	32	55	13	0
Region 6. North Central	33	22	33	0
Region 7. Western	42	58	0	0
Occurrence in U.S. groundwater sources				
Region 1. New England	71	21	7	0
Region 2. Mid-Atlantic	81	4	11	4
Region 3. South East	82	14	2	0
Region 4. Midwest	40	40	15	5
Region 5. South Central	68	27	15	0
Region 6. North Central	30	40	30	0
Region 7. Western	24	34	28	14
Occurrence in U.S. finished surface water supplies				
Region 1. New England	88	12	0	0
Region 2. Mid-Atlantic	92	8	0	0
Region 3. South East	100	0	0	0
Region 4. Midwest	73	27	0	0
Region 5. South Central	74	19	7	0
Region 6. North Central	44	44	0	12
Region 7. Western	42	58	0	0
Occurrence in U.S. finished groundwater supplies				
Region 1. New England	79	21	0	0
Region 2. Mid-Atlantic	81	4	11	4
Region 3. South East	94	4	2	0
Region 4. Midwest	58	27	12	3
Region 5. South Central	61	27	12	0
Region 6. North Central	40	50	10	0
Region 7. Western	20	40	22	12

[a]National Arsenic Occurrence Survey - Frey and Edwards 1997

of municipal supplies. The highest arsenic levels in New Hampshire are associated with bedrock wells in the south eastern and south central part of the state. In a recent study of arsenic in well water supplies in Saskatchewan, Canada, 13% of samples were >20 µg/L and one sample exceeded 100 µg/L (Thompson et al. 1999). It was noted that the samples with high arsenic levels were derived from sites that were in near proximity to each other, indicating the presence of 'hot spots' with similar geological characteristics. The Lower Rio Grande Valley Environmental Study (LRGVES), conducted during the spring and summer of 1993, was designed to evaluate multiple forms of exposure to environmental contaminants by Valley residents (Berry et al. 1997). As a part of the study, drinking and household water samples were collected from nine residences and analyzed for contaminants including arsenic. The sources of water available in the residences were public treatment facilities, vended water machines, and a private well. Levels of arsenic ranged from 1.1 to 4.5 µg/L with a median of 3.4 µg/L. None of the samples exceeded the EPA MCL of 50 µg/L for public drinking water supplies (EPA 1993a). As part of an epidemiological study, Engel and Smith (1994) investigated the levels of arsenic in drinking water throughout the United States between 1968 and 1984. They found that 30 counties in 11 states had mean arsenic levels of more than 5 µg/L, with a range of 5.4–91.5 µg/L; 15 counties had mean levels from 5 to 10 µg/L; 10 counties had mean levels from 10 to 20 µg/L; and 5 counties had levels greater than 20 µg/L. The highest levels were found in Churchill County, Nevada, where 89% of the population were exposed to a mean arsenic concentrations of 100 µg/L and 11% to a mean of 27 µg/L.

Many communities have high levels of arsenic in their drinking water because of contamination or as a result of the geology of the area. In Millard County, Utah, seven towns had median and maximum arsenic levels of 18.1–190.7 µg/L and 125–620 µg/L, respectively, in their drinking water (Lewis et al. 1999). The mean arsenic concentration in tap water from homes in Ajo, Arizona, about two miles from an open pit copper mine and smelter was 90 µg/L (Morse et al. 1979). The town's water was supplied from five deep wells. A municipal water supply system in the vicinity of a former copper smelter in Anaconda, Montana, had an arsenic level of 1.36 µg/L (Hwang et al. 1997a). Most of the private wells that were sampled in the area had arsenic levels below 5 µg/L, with an average of 2.5 µg/L.

Durant et al. (1995) hypothesized that due to a previously unrecognized mobilization of toxic metals from a waste disposal site, residents of Woburn, Massachusetts, may have been exposed to arsenic at levels of 70 µg/L between 1966 and 1986. This level is higher than the federal drinking water standard of 50 µg/L (EPA 1993a). However, the same investigators working with others (Rogers et al. 1997) later found that the arsenic levels in hair samples donated by Woburn residents were not consistent with the hypothesized arsenic level and suggested that the water arsenic levels were lower than first estimated.

Some developing countries, such as Mexico, Bangladesh, and India have highly elevated levels of arsenic in drinking water in some regions (Bagla and Kaiser 1996; Tondel et al. 1999; Wyatt et al. 1998a, 1998b). In Bangladesh and West Bengal, the soil naturally contains high levels of arsenic which leaches into the shallow groundwater that is tapped for drinking water. In West Bengal, India, it is estimated that more than one million Indians are drinking arsenic-laced water and tens of millions more could be at risk in areas that have not been tested for contamination. Analysis of 20,000 tube-well waters revealed that 62% have arsenic at levels above the World Health Organization (WHO) permissible exposure limit (PEL) of 10 µg/L, with some as high as 3,700 µg/L (Bagla and Kaiser 1996). Several investigators have noticed a correlation between high levels of arsenic and fluoride in drinking water (Wyatt et al. 1998a, 1998b).

5.4.3 Soil

Arsenic is found in the earth's crust at an average level of 2 µg/g (ppm) (NAS 1977b). Arsenic in soil may originate from the parent materials that form the soil, industrial wastes, or use of arsenical pesticides. Geological processes that may lead to high arsenic concentrations in rock and subsequently the surrounding soil include hydrothermic activity and pegmetite formation (Peters et al. 1999). In the first case thermal activity results in the dissolution and transport of metals, such as arsenic, which are precipitated in fractures in rocks. In the second process, cooling magmas may concentrate metals which are injected into rocks, crystallizing as pegmatites. Areas of volcanic activity include large areas of California, Hawaii, Alaska, Iceland, and New Zealand.

Background arsenic concentrations in soil range from about 1 to 40 µg/g, with a mean value of about 5 µg/g (Beyer and Cromartie 1987; Eckel and Langley 1988; EPA 1982b; NAS 1977a). The U.S. Geological Survey reports the mean and range of arsenic in soil and other surficial materials as 7.2 and <0.1–97 µg/g, respectively (USGS 1984). The concentrations of arsenic in 445 Florida surface soils ranged from 0.01 to 50.6 µg/g (Chen et al. 1999). The median, arithmetic mean, and geometric mean were 0.35, 1.34±3.77, and 0.42±4.10 µg/g, respectively. The geometric mean arsenic concentration in 50 California soils was 2.8 µg/g (Chen et al. 1999). In the Florida surface soils, arsenic was highly correlated (α=0.0001) with the soil content of clay, organic carbon, CEC, total iron, and total aluminum. Arsenic tends to be associated with clay fractions and iron and manganese oxyhydroxides. Soils of granitic origin are generally low in arsenic, about 4 µg/g, whereas arsenic in soils derived from sedimentary rocks may be as high as 20–30 µg/g (Yan-Chu 1994). Soils overlying arsenic-rich geologic deposits, such as sulfide ores, may have soil concentrations two orders of magnitude higher (NAS 1977a).

Soils in mining areas or near smelters may contain high levels of arsenic. Arsenic concentrations up to 27,000 µg/g were reported in soils contaminated with mine or smelter wastes (EPA 1982b). Soils at an abandoned mining site in the Tamar Valley in southwest England have arsenic concentration that may exceed 50,000 µg/g (Erry et al. 1999). The average arsenic levels in the top 2 cm of different soil types in the vicinity of a former copper smelter in Anaconda, Montana, ranged from 121 to 236 µg/g; levels were significantly related to proximity and wind direction to the smelter site (Hwang et al. 1997a). Smelter fallout can contaminate land miles from the source. The source of elevated arsenic levels in soil in the Mexican community of Anapra in Ciudad Juarez, Chihuahua, was a lead smelter in El Paso, Texas, that ceased operation in 1985. Three geographical locations varying in distance from the smelter source were evaluated for arsenic levels in the soil. Mean arsenic levels of the three sectors at increasing distance from the source were 25.2 µg/g (n=8), 21.4 µg/g (n=7), and 19.5 µg/g (n=4). Soil from a control area located 25 km away from the smelter had a mean concentration of 8.6 µg/g (n=3) (Diaz-Barriga et al. 1997).

Soil on agricultural lands treated with arsenical pesticides may retain substantial amounts of arsenic. One study reported an arsenic concentration of 22 µg/g in treated soil compared to 2 µg/g for nearby untreated soil (EPA 1982b). Arsenic was measured in soil samples taken from 10 potato fields in Suffolk County on Long Island, New York, where sodium arsenite had been used for vine control and fall weed control for many years. Lead arsenate also may have been used as an insecticide in certain areas. The mean arsenic levels taken at a depth of 0–18 cm from each of the 10 fields ranged from 27.8±5.44 µg/g dry weight (n=10) to 51.0±7.40 µg/g dry weight (n=10). These levels were markedly higher than the level of 2.26±0.33 µg/g (n=10) for untreated control soils (Sanok et al. 1995). A survey was conducted in 1993 to determine the concentrations of arsenic and lead in soil samples from 13 old orchards in New York State. Lead arsenate was used for pest control in fruit orchards for many years mainly from the 1930s to 1960s and residues remain in the soil. Concentrations of arsenic ranged from 1.60 to 141 µg/g dry weight (Merwin et al. 1994).

Contamination by heavy metals is a serious problem in some developing countries. Sepetiba Bay, a semi-enclosed coastal lagoon in Brasil, had sediment arsenic concentrations up to 80,000 µg/g in an area adjacent to a plant that produced zinc and cadmium (Moreira 1996). The plant uses ~1,500 tons of arsenic per year to purify the electrolytic solution used in the production of these metals. In Zimbabwe, surface soil (~10 cm depth) at abandoned mine dumps contained arsenic at an average concentration of 9,530±250 µg/g. Soil near a river stream about 400 meters from the mine dumps contained 550±40 µg/g of arsenic (Jonnalagadda and Nenzou 1996).

Sediment arsenic concentrations reported for U.S. rivers, lakes, and streams range from about 0.1 to 4,000 µg/g (Eisler 1994; Heit et al. 1984; NAS 1977a; Welch et al. 1988). During August through November 1992 and August 1993, bed sediment in the South Platte River Basin (Colorado, Nebraska, Wyoming) was sampled and analyzed for 45 elements, including arsenic. The range of arsenic found was 2.8–31 µg/g dry weight, and the geometric mean (n=23) was 5.7 µg/g (Heiny and Tate 1997). The arsenic concentration in surficial sediment (0–2 cm) at 43 sites in the Indian River Lagoon System in Florida ranged from 0.6 to 15 µg/g dry weight with a mean of 5.0±3.9 µg/g (Trocine and Trefry 1996). Arsenic levels were well correlated with those of aluminum. Correlation with aluminum levels is used to normalize sediment level concentrations to natural levels in Florida estuaries. Surficial sediments collected from 18 locations in 3 major tributaries to Newark Bay, New Jersey, were analyzed for 7 toxic metals, including arsenic (Bonnevie et al. 1994). The highest concentrations of arsenic were found in the Rahway River adjacent to a chemical plant, 58 µg/g dry weight, and in the Hackensack River adjacent to a coal-fired power plant, 49 µg/g. The average arsenic concentration for all sediments was 17±16 µg/g. Sediments collected from seven sites in Baltimore Harbor, Maryland, at five seasonal periods between June 1987 and June 1988 had a geometric mean maximum of 7.29 µg/g dry weight and a geometric mean minimum of 1.25 µg/g (Miles and Tome 1997). This harbor is one of two sub-tributaries of the Chesapeake Bay where contaminants have been discharged on a large scale. Metal concentrations have been measured in sediments from the Times Beach Confined Disposal Facility, an area of documented chemical contamination in Buffalo, New York (Roper et al. 1996); arsenic concentrations ranged from 27.5 to 54.0 µg/g dry weight.

The upper Clark Fork River basin in western Montana is widely contaminated by metals from past mining, milling, and smelting activities. In a 1991 study, arsenic levels were determined in sediment along the river and in a reservoir 205 km downstream. Total arsenic in sediments from Clark Fork River decreased from 404 µg/g (dry weight) at the farthest upstream sampling station to 11 µg/g, 201 km downstream. Sediment samples from the Milltown Reservoir had arsenic concentrations ranging from 6 to 56 µg/g (Brumbaugh et al. 1994). Total recoverable arsenic in nonfiltered pore water from the Clark Fork River decreased from 1,740 µg/L at the farthest upstream sampling station to 31 µg/L at 201 km station (Brumbaugh et al. 1994). The Coeur d'Alene river basin in northern Idaho has been contaminated with heavy metals from mining and smelting operations since 1885 (Farag et al. 1998). A 1994 study determined the metal content of sediment, biofilm, and invertebrates at 13 sites in the basin, 10 with historic mining activity and 3 reference sites. The mean arsenic levels in sediment at the mining sites ranged from 8.3 to 179.0 µg/g (dry weight), compared with 2.4 to 13.1 µg/g (dry weight) at the reference sites. The mean arsenic levels in biofilm adhering to rock in the water at the mining sites ranged from

7.5 to 155.8 µg/g (dry weight), compared with 7.2 to 27.3 µg/g (dry weight) at the reference sites. In Whitewood Creek, South Dakata, where as much as 100 million tons of mining and milling waste derived from gold mining activities were discharged between 1876 and 1977, mean and maximum sediment arsenic concentrations were 1,920 and 11,000 µg/g, respectively (Goddard 1987). Uncontaminated sediment had mean arsenic levels of 9.2 µg/g. Swan Lake, a sub-bay of Galveston Bay in Texas is a highly industrial area that received runoff from a tin smelter in the 1940s and 1950s. Surface sediments at 17 sites where oysters and mussels were collected ranged from 4.53 to 103 µg/g (Park and Presley 1997). A site in the channel leading from the old smelter had arsenic levels of 568 µg/g. Surface sediment was less contaminated than deeper sediment, indicating less arsenic input recently than in the past as a result of the smelter closing.

It has recently been suggested that the wood preservative most commonly used in dock pilings and bulkheads (chromated copper arsenate) can be toxic to estuarine organisms. Wendt et al. (1996) measured arsenic in surficial sediments and oysters from creeks with high densities of docks and from nearby reference creeks with no docks. The average concentrations in the sediments ranged from 14 to 17 µg/g throughout the study area, which is within the range of natural background levels.

5.4.4 Other Environmental Media

Background arsenic levels in living organisms are usually <1 µg/g wet weight (Eisler 1994). Levels are higher in areas with mining and smelting activity or where arsenical pesticides were used. Eisler (1994) has an extensive listing of arsenic levels in terrestrial and aquatic flora and fauna from literature sources to about 1990. The U.S. Fish and Wildlife Service's national Contaminant Biomonitoring Program have analyzed contaminants in fish at 116 stations (rivers and the Great Lakes) across the United States. The geometric mean concentration of arsenic for the five collection periods starting in 1976 were (period, concentration wet weight basis): 1976–1977, 0.199 µg/g; 1978–1979, 0.129 µg/g; 1980–1981, 0.119 µg/g; 1984, 0.106 µg/g; 1986, 0.083 µg/g (Schmitt et al. 1999). In 1986, the maximum and 85th percentile arsenic levels were 1.53 and 0.24 µg/g, respectively. The highest concentrations of arsenic for all five collection periods were in bloaters from Lake Michigan at Sheboygan, Wisconsin. Arsenic levels declined by 50% at this site between 1976–1997 and 1984. The major source of arsenic into Lake Michigan was a facility at Marinette, Wisconsin that manufactured arsenic herbicides. Table 5-3 contains arsenic levels in aquatic organisms from more recent studies. The Coeur d'Alene river basin in northern Idaho has been contaminated with heavy metals from mining and smelting operations since 1885 (Farag et al. 1998). A 1994 study determined the metal content of sediment, biofilm, and invertebrates at

Table 5-3. Levels of Arsenic in Fish and Shellfish—Recent Studies

Sample type	Arsenic concentration[a] (µg/g)	Comments	Reference
Fish liver (composite samples)		South Platt River Basin 1992–1993	Heiny and Tate 1997
Brown trout (n=4)	GM 0.40, range <0.1–0.68		
White sucker (n=10)	GM 0.34, range <0.1–0.76		
Common carp (n=10)	GM 0.27, range <0.1–0.87		
Yellowtail flounder		Samples collected from Northwest Atlantic 1993	Hellou et al. 1998
Muscle (n=8)	8–37		
Liver (n=6)	7–60		
Gonad (n=6)	1.2–9.4		
Marine organisms		Belgian fish markets in 1991 Inorganic arsenic ranged from 0.003 to 0.2 µg/g.	Buchet and Lison 1998
Ray (n=8)	16.4		
Cod (n=8)	4.7		
Plaice (n=8)	19.8		
Sole (n=8)	5.1		
Sea-bream (n=8)	2.4		
Mussell (n=8)	3.5		
Bluefin tuna (*Thunnus thynus*) (n=14)	3.2	Virgin Rocks, Grand Banks of Newfoundland, Canada, 1990	Hellou et al. 1992
Fish		National Contaminant Biomonitoring Program, 1984–1985,112 stations	Kidwell et al. 1995
Bottom feeding (n=2,020)	0.16±0.23 wet weight		
Predatory(n=12)	0.16±0.140 wet weight		
Bivalve mollusks		Kuala Lumpur, Malaysia, 1993, 5 fish stores	Mat 1994
A. granosa	4.65–5.30 wet wt, range of means		
P. undulata	3.84–4.42 wet wt range of means		
Benthic invertebrate composites	GM maximum 15.4 GM minimum 6.14 maximum measure 1.3	Baltimore Harbor, Maryland, 1987–1988	Miles and Tome 1997
Oysters		South Carolina, private residential docks on tidal creeks, 1994	Wendt et al. 1996
<1 m from docks (n=10)	8.3±1.1		
>10 m from docks (n=10)	7.6±0.9		
Reference (no docks) (n=10)	8.4±1.3		
Clams (n=22)	12±1.1	Indian River Lagoon, Florida, 22 sites, 1990	Trocine and Trefry 1996

Table 5-3. Levels of Arsenic in Fish and Shellfish—Recent Studies *(continued)*

Sample type	Arsenic concentration[1] (µg/g)	Comments	Reference
Marine organisms		Swan Lake, Galveston Bay, Texas, 1993	Park and Presley 1997
Snails	13.3±17.0		
Blue crab	6.61		
Fish	0.82		
Shrimp	1.37±0.64		
Whole crab	5.35±2.51		
Oysters (n=10, pooled)	7.28±1.32		
Mussels (n=7, pooled)	7.75±2.15		
Marine Organisms		GPNEP, 1992, Galveston Bay, Texas	Park and Presley 1997
Blue crab	2.31±2.15		
Fish	2.46		
Oysters, 2 areas		NOAA NS&T Program, 1986–1990	Park and Presley 1997
n=78, pooled	4.50±1.08	Galveston Bay	
n=874, pooled	9.67±7.00	Gulf of Mexico	

GM = geometric mean; GPNEP = Galveston Bay National Estuary Program; NOAA NS&T = National Oceanic and Atmospheric Administration National Status and Trends

[a]Concentrations are means ± standard deviation, unless otherwise stated. Concentrations are in a dry weight basis, unless otherwise stated.

13 sites in the basin, 10 with historic mining activity and 3 reference sites. The mean arsenic levels in benthic macroinvertebrates at the mining sites ranged from 2.2 to 97.0 µg/g (dry weight), compared with 2.1 to 2.4 µg/g (dry weight) at the reference sites. A study of aquatic organism in Swan Lake, a highly polluted sub-bay of Galveston Bay, Texas showed that arsenic concentrations were in the order snail>oyster>crab>shrimp>fish (Park and Presley 1997). In contrast to metals like silver, cadmium, copper, and zinc, arsenic concentrations in oysters and mussels were less than in the sediment from which they were collected. No significant correlation was found between levels of arsenic in clams in the Indian River Lagoon in Florida with those found in sediment or water samples (Trocine and Trefry 1996). Small animals living at mining sites ingest more arsenic in their diet and have higher arsenic levels in their bodies than those living on uncontaminated sites (Erry et al. 1999). Seasonal variations in both arsenic intake and dietary composition may affect the amount of arsenic taken up by the body and transferred to predator animals. Tissue arsenic content of wood mice and bank voles living on both arsenic-contaminated mining sites and uncontaminated sites were greater in autumn than spring. The lower tissue arsenic levels in spring of rodents living on contaminated sites suggests that there is no progressive accumulation of arsenic in overwintering animals.

Low levels of arsenic are commonly found in food; the highest levels are found in seafood, meats, and grains. Typical U.S. dietary levels of arsenic in these foods range from 0.02 ppm in grains and cereals to 0.14 ppm in meat, fish, and poultry (Gartrell et al. 1986). Shellfish and other marine foods contain the highest arsenic concentrations and are the largest dietary source of arsenic (Gunderson 1995a; Jelinek and Corneliussen 1977; Tao and Bolger 1999). Marine organisms appear to have the ability to accumulate arsenic naturally present in seawater and food, rather than due to local pollution (Eisler 1994). Arsenic levels in fish and seafood are usually about 4–5 ppm (Bennett 1986; Schroeder and Balassa 1966), but may be as high as 170 ppm (NAS 1977b). Arsenic levels are also high, 10–109 mg/kg dry weight, in seaweeds (Eisler 1994). In the U.S. Food and Drug Administration (FDA) Total Diet Study, 1991–1997, seafood contained the highest levels of arsenic, followed by rice/rice cereal, mushrooms, and poultry. Concentrations in canned tuna (in oil), fish sticks, haddock (pan-cooked), and boiled shrimp were 0.609–1.470, 0.380– 2.792, 0.510–10.430, and 0.290–2.681 ppm, respectively (Tao and Bolger 1999). Typically, arsenic levels in foods in the Total Diet Study were low, less than 0.03 ppm; only 63 of the 264 foods contained arsenic above this level. It is important to bear in mind that much of the arsenic in fish, shellfish and seaweed is present as relatively nontoxic organoarsenical compounds, usually arsenobetaine which does not appear to be harmful to humans and is excreted, rapidly and unchanged, in urine (Cullen 1998; Dabeka et al. 1993; Eisler 1994; Gebel et al. 1998b). However, some of the arsenic in these foods are in inorganic form. For example, a recent study in the Netherlands reported that

inorganic arsenic comprised 0.1–41% of the total arsenic in seafood (Vaessen and van Ooik 1989). Buchet et al. (1994) found that, on the average, 3% of the total arsenic in mussels was inorganic in form. Based upon data in the literature, MacIntosh et al. (1997) estimated that inorganic arsenic accounts for 1.5% of total arsenic in fish and 20% of total arsenic in shellfish. Schoof et al. (1998) found considerable variability in the total arsenic and inorganic arsenic content of Taiwanese rice and yams. Roughly three quarters of the arsenic in the samples were inorganic arsenic.

In the Lower Rio Grande Valley Environmental Study, 6 of 30 local food items and replicates collected in the spring of 1993 had arsenic concentrations above the detection limit, ranging from 0.032 to 2.65 µg/g (Berry et al. 1997). MacIntosh et al. (1997) estimated dietary intake of inorganic arsenic and found that 91 food items each contributed at least 0.05% to the intake of total inorganic arsenic. The 35 food items with the highest inorganic arsenic concentrations accounted for 90% of the estimated inorganic arsenic consumption. White rice and shrimp accounted for approximately 15 and 11%, respectively. Nriagu and Lin (1995) analyzed 26 brands of wild rice sold in the United States and found arsenic levels ranging from 0.006 to 0.142 µg/g dry weight.

During a comprehensive total diet study extending from 1985 to 1988, foods were collected in six Canadian cities and processed into 112 composite food samples (Dabeka et al. 1993). The mean, median, and range of total arsenic in all samples were 0.0732, 0.0051, and <0.0001–4.840 µg/g, respectively. Food groups containing the highest mean arsenic levels were fish (1.662 µg/g), meat and poultry (0.0243 µg/g), bakery goods and cereals (0.0245 µg/g), and fats and oils (0.0190 µg/g). Of the individual samples, marine fish had the highest arsenic levels, with a mean of 3.048 µg/g for the cooked composites and 2.466 µg/g for the raw samples. Canned fish (1.201 µg/g) and shellfish (2.041 µg/g) also contained high means. Cooked poultry, raw mushrooms, and chocolate bars contained 0.100, 0.084, and 0.105 µg/g, respectively.

A Danish study (Pedersen et al. 1994) reports the arsenic levels in beverages as the mean (range) in µg/L as follows: red wine, 9 (<2–25); white wine, 11 (<2–33); fortified wine, 5 (<2–11); beer, 7 (4–11); soft drinks, 3 (<2–8); miscellaneous juices, 8 (3–13); instant coffee, 4 (0.7–7); and instant cocoa, 5.6 (1.6–12.8).

Most studies of dietary intake of arsenic are done on the basis of total arsenic, which is dominated by relatively nontoxic organic forms of arsenic. Schoof et al. (1999a) reported on the analysis of 40 commodities anticipated to account for 90% of dietary inorganic arsenic intake. Consistent with

earlier studies, total arsenic concentrations were highest in the seafood sampled (ranging from 160 ng/g in freshwater fish to 2,360 ng/g in marine fish). In contrast, average inorganic arsenic in seafood ranged from <1 to 2 ng/g. The highest inorganic arsenic concentrations were found in raw rice (74 ng/g), followed by flour (11 ng/g), grape juice (9 ng/g), and cooked spinach (6 ng/g). Schoof et al. (1999b) estimated that intake of inorganic arsenic in the U.S. diet ranges from 1 to 20 µg/day, with a mean of 3.2 µg/day.

Tobacco contains an average arsenic concentration of 1.5 ppm, or about 1.5 µg per cigarette (EPA 1998j). Before arsenical pesticides were banned, tobacco contained up to 52 mg As/kg, whereas after the ban, maximum arsenic levels were reduced to 3 µg/g (Kraus et al. 2000). An international literature survey reports arsenic yields of 0 to 1.4 µg/cigarette for mainstream (inhaled) cigarette smoke (Smith et al. 1997). The wide range of arsenic yields for flue-cured cigarettes suggests that the field history, soil, and fertilizer conditions under which the tobacco is grown will affect the arsenic concentration (Smith et al. 1997). Arsenic emission factors of 0.015 to 0.023 µg/cigarette (mean 0.018±0.003 µg/cigarette) have been measured for sidestream smoke from a burning cigarette (Landsberger and Wu 1995).

Arsenic has also been detected in several homeopathic medicines at concentrations up to 650 µg/g (Kerr and Saryan 1986). Some Chinese proprietary medicines that are manufactured in China, Hong Kong, and other Asian countries have been reported to contain levels of inorganic arsenic ranging from 25 to 107,000 µg/g (Chan 1994). Fifty medicinally important leafy samples that were analyzed for elemental concentrations contained arsenic at levels ranging from 0.12 to 7.36 µg/g, with a mean of 2.38±1.2 µg/g (Reddy and Reddy 1997).

The possible presence of toxic compounds in waste materials has raised concerns about the fate of these compounds either during the composting process or when the composted product is applied to soils. Three waste compost products generated at the Connecticut Agricultural Experiment Station had arsenic levels of 12.8, 9.8, and 13 µg/g dry weight, respectively (Eitzer et al. 1997). The arsenic levels in municipal solid waste composts from 10 facilities across the United States ranged from 0.9 to 15.6 µg/g (dry weight) with a mean of 6.7 µg/g (He et al. 1995). These are lower than the EPA 503 regulatory limit for arsenic of 41 µg/g for agricultural use of sewage sludge (EPA 1993b). Concentrations of arsenic in U.S. sewage sludges, which are sometimes spread on soil, were <1 µg/g. Arsenic is a common impurity in minerals used in fertilizers. A comprehensive Italian study found that the arsenic content in a number of mineral and synthetic fertilizers ranged from 2.2 to 322 mg/kg with a sample of triple superphosphate having the highest level (Senesi et al. 1999). Arsenic naturally occurs in coal and crude oil at levels of

0.34–130 and 0.0024–1.63 ppm, respectively, which would account for its presence in flue gas, fly ash, and bottom ash from power plants (Pacyna 1987).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Exposure to arsenic may include exposure to the more toxic inorganic forms of arsenic, organic forms of arsenic, or both. While many studies do not indicate the forms of arsenic people are exposed to, one may often infer this information from the source of exposure (e.g., fish contain organic arsenic). Environment Canada (1993) estimated the intake of the more toxic inorganic arsenic from air, water, food, and ingesting dirt for various age groups of the general population and for those living near point sources. Their results are shown in Table 5-4. For the general population, food is usually the greatest source of arsenic exposure. For inorganic arsenic, food also represents the principal route of intake for all age groups (<0.02–2.0 µg/kg-body weight per day), followed by ingesting dirt for infants and children (0.02–0.08 µg/kg-body weight per day), and water and air for all age groups. Based on limited data, the average daily intake of inorganic arsenic from surface water supplies of drinking water by all age groups is generally <0.5 µg/kg-body weight per day. Intake may be higher from some groundwater supplies. Average daily intakes from ambient air is estimated to range from 0.0003 to 0.0004 µg/kg-body weight per day bringing the range of total daily exposure to inorganic arsenic to 0.1–2.6 µg/kg-body weight per day.

Drinking water may also be a significant source of arsenic exposure in areas where arsenic is naturally present in groundwater. While estimates of arsenic intake for typical adults drinking 2 liters of water per day average about 5 µg/day (Environment Canada 1993; EPA 1982c), intake can be much higher (10–100 µg/day) in geographical areas with high levels of arsenic in soil (see Figure 5-2). It is assumed that nearly all arsenic in drinking water is inorganic (EPA 1984a).

In the United States, food intake of arsenic has been estimated to range from 2 µg/day in infants to 92 µg/day in 60–65-year-old men (see Table 5-5) (Tao and Bolger 1999). The average intake of *inorganic* arsenic ranges from 1.34 µg/day in infants to 12.54 µg/day in 60–65-year-old men. The greatest dietary contribution to total arsenic was seafood (76–96%) for all age groups, except infants. For infants, seafood and rice products contributed 42 and 31%, respectively. Adult dietary arsenic intakes reported for other countries range from 11.7 to 280 µg/day (Tao and Bolger 1999). Seafood is estimated to be mostly (80–99%) present as non-toxic organic forms.

Table 5-4. Estimated Mean Daily Intake of Inorganic Arsenic

	Estimated daily intake (µg/kg body weight per day)				
Medium	0–0.5 years[a]	0.5–4 years[b]	5–11 years[c]	12–19 years[d]	Adult[e]
Unexposed Population					
Water[f]	0.08	0.3	0.2	0.1	0.1
Food[g]	<0.04–2.4	<0.05–2.0	<0.03–1.9	<0.02–1.2	0.02–0.6
Air[h]	0.0003	0.0004	0.0004	0.0004	0.0003
Soil/Dirt[i]	0.03–0.08	0.02–0.05	0.006–0.02	0.002–0.005	0.001–0.004
Total	0.1–2.6	0.3–2.4	0.2–2.1	0.1–1.3	0.1–0.7
Population Living Near Point Sources					
Water[f]	<0.08–8.3	<0.3–31	<0.2–20	<0.1–10	<0.1–11
Food[g]	<0.04–2.4	<0.05–2.0	<0.03–1.9	<0.02–1.2	0.02–0.6
Air	0.003–0.07	0.003–0.085	0.004–0.10	0.003–0.08	0.0025–0.06
Soil/Dirt[i]	0.02–3.0	0.01–1.9	0.004–0.6	0.001–0.2	0.0009–0.1
Total	<0.1–14	<0.4–35	<0.2–23	<0.1–11	<0.1–12

Source: Environment Canada 1993

[a]Weight 6 kg; 2 m^3 air/day; 0.1 L water/day; ingest 35 mg soil/day
[b]Weight 13 kg; 5 m^3 air/day; 0.8 L water/day; ingest 50 mg soil/day
[c]Weight 27 kg; 12 m^3 air/day; 1.1 L water/day; ingest 35 mg soil/day
[d]Weight 55 kg; 21 m^3 air/day; 1.1 L water/day; ingest 20 mg soil/day
[e]Weight 70 kg; 20 m^3 air/day; 1.5 L water/day; ingest 20 mg soil/day
[f]Assumed water concentration to be 5 Fg/L in nonsource areas.
[g]Estimated that 37% of intake from food is inorganic. Unable to estimate intake from breast milk.
[h]Assumed air concentration 0.001 Fg/m^3 in nonsource areas.
[i]Range of arsenic in Canadian soil types is 4.8–13.6 ppm, all of which is inorganic.

Table 5-5. Mean Daily Dietary Intake of Arsenic for Selected Population Groups

	Mean daily intake (µg/kg body weight per day)								
Date of study	PTDI[a]	6–11 month	2 years	14–16 years F	14–16 years M	25–30 years F	25–30 years M	60–65 years F	60–65 years M
1984–1986[b]	2.1	0.82	1.22	0.54	0.60	0.66	0.76	0.71	0.74
1986–1991[c]	2.1	0.5	0.81	0.36	0.39	0.44	0.51	0.46	0.48
1991–1997[d]	2.1	0.31	1.80	0.41	0.24	0.44	0.72	1.08	1.14

[a]No agreement has been reached on a maximum acceptable intake for total arsenic; the FAO/WHO has assigned a PTDI for inorganic arsenic of 2.1 µg/kg body weight for adults.
[b]Gunderson 1995a
[c]Gunderson 1995b
[d]Tao and Bolger 1999

F = female; M = male; PTDI = Provisional Tolerable Daily Intake

The FDA conducted earlier Total Diet Studies in 1984–1986 and 1986–1991. For the sampling period of June 1984 to April 1986, the total daily intake of arsenic from foods was 58.1 µg for a 25–30-year-old male with seafood contributing 87% of the total (Gunderson 1995a). For the sampling period July 1986 to April 1991, the total daily intake of arsenic from foods was lower, 38.6 µg for a 25–30-year-old male. Seafood again was the major source of arsenic, contributing 88% of the total (Gunderson 1995b). Results of the two Total Diet Studies for selected population groups are shown in Table 5-5. The Total Diet Study for the sampling period of September 1991 to December 1996, shows that arsenic, at $0.03 µg/g, was found in 55 (21%) of the 261–264 foods/mixed dishes analyzed. The highest concentrations again were found in seafood, followed by rice/rice cereal, mushrooms, and poultry. The estimated total daily intake of arsenic from foods was 56.6 µg for a 25–30-year-old male. Seafood was the major contributor, accounting for 88–96% of the estimated total arsenic intake of adults. The dietary intake of inorganic arsenic is estimated to range from 8.3 to 14 µg per day (NRC 1999).

Average daily dietary exposures to arsenic were estimated for approximately 120,000 U.S. adults by combining data on annual diet, as measured by a food frequency questionnaire, with residue data for table-ready foods that were collected for the annual FDA Total Diet Study. Dietary exposures to arsenic were highly variable, with a mean of 50.6 µg/day (range, 1.01–1,081 µg/day) for females and 58.5 µg/day (range, 0.21–1,276 µg/day) for males (MacIntosh et al. 1997). Inorganic arsenic intake in 969 men and women was assessed by a semi-quantitative food frequency questionnaire in combination with a database for arsenic content in foods and by toenail concentrations of arsenic. The mean estimated average daily consumption of inorganic arsenic was 10.22 µg/day, with a standard deviation of 6.26 µg/day and a range of 0.93–104.89 µg/day (MacIntosh et al. 1997).

During a comprehensive total diet study extending from 1985 to 1988, the estimated daily dietary ingestion of total arsenic by the average Canadian was 38.1 µg and varied from 14.9 µg for the 1–4 year-old-age group and 59.2 µg for 20–39-year-old males (Dabeka et al. 1993). Daily intakes of arsenic from food by women in the Shiga Prefecture, Japan, were investigated by the duplicate portion method and by the market basket method. In 1991 and 1992, the daily intakes determined by the duplicate portion method were 206 and 210 µg, respectively. Those determined by the market basket method were 160 and 280 µg, respectively (Tsuda et al. 1995b).

The arsenic concentration in the breast milk of 35 women in Ismir, Turkey, a volcanic area with high thermal activity ranged from 3.24 to 5.41 µg/L, with a median of 4.22 µg/L (Ulman et al. 1998). The mean arsenic levels in three groups of cows in the region that grazed on land impacted by lava and

thermal activity were 4.71, 4.46, and 4.93 µg/L, compared to 5.25 µg/L for cows kept in sheds and fed commercial pellet feed and municipal water.

A Danish study found that carrots grown on soil containing 30 µg/g of arsenic, which is somewhat above the 20 µg/g limit for total arsenic set by Denmark for growing produce, contained 0.014 µg/g fresh weight of arsenic, all in the form of inorganic As(III) and As(V) (Helgesen and Larsen 1998). An adult consuming 376 grams of vegetable a day (90^{th} percentile) represented solely by carrots would consume 5.3 µg of arsenic a day. The study concluded that the estimated intake of arsenic from produce grown in soil meeting regulatory limits was low compared with other food sources and water.

If vegetables are grown in planters made of wood treated with CCA, arsenic may leach out of the wood and be taken up by the vegetables. While no studies have been found on this potential source of exposure, other studies indicate that uptake of arsenic from soil is generally not very high. In addition, food grown in this manner is unlikely to constitute a significant part of a person's diet.

A German study investigated the transfer of arsenic from the environment to humans in the northern Palatine region, a former mining area characterized by high levels of arsenic (<2–605 µg/g) in residential areas compared to a region in southern lower Saxony with nonelevated levels of arsenic in soil (Gebel et al. 1998a). None of the residents were occupational exposed to arsenic and the arsenic levels in drinking water were generally below 0.015 mg/L. Therefore increased exposure to arsenic would only be caused by the soil and home-grown produce. The mean levels of arsenic in urine and hair were lower in the reference area than in the former mining area (see Table 5-6), although within the mining area there was a slight increase in arsenic levels in hair and arsenic excreted in urine with increasing arsenic content in soil. Children in the Palatine region also did not show higher contents of arsenic in their hair or urine. The most significant factor contributing to elevated levels of arsenic in hair and urine was seafood consumption. In the combined population of people living in mining areas containing high levels of arsenic in soil and other areas, the level of arsenic in urine was positively associated with the extent of seafood consumption. However, the study also showed that seafood consumption does not lead to an extreme increase in excretion of arsenic in the urine. There are apparently other, unidentified factors affecting the urine levels. Only arsenic in urine, not in hair, was significantly correlated with age. The level of arsenic in urine was very slightly, but significantly correlated with the consumption of home-grown produce. Tobacco smoking had no correlation with the arsenic content of either hair or urine (Gebel et al. 1998a).

Table 5-6. Levels of Arsenic in Human Tissue and Urine—Recent Studies

Site	Population	Sample	Concentration		Units	Reference
			Mean[a]	Range		
Fort Valley, Georgia, Pesticide mfg facility (Superfund site)	40 workers (samples collected at end of work week)	Urine, random	11.6	<1–57	µg/L	Hewitt et al. 1995
		Urine, 24-hour	11.0	<1–54	µg/L	
		Hair	0.78	<0.01–6.3	µg/g	
		Fingernails	0.79	<0.01–6.1	µg/g	
Hermosa, Sonora, Mexico	Children, ages 7–11, exposed to arsenic in water (mean concn [mean dose]):	Urine, 24-hour				Wyatt et al. 1998a, 1998b
	9 µg/L [0.481µg/kg/day]		10.26	4.05–19.68	µg/day	
	15 µg/L [0.867 µg/kg/day]		10.54	2.82–20.44	µg/day	
	30 µg/L [1.92 µg/kg/day]		25.18	5.44–93.28	µg/day	
Glasgow, Scotland	Adults, normal (n=1250)	Hair	0.650	0.20–8.17	µg/g	Raie 1996
	Adults, postmortem (n=9)	Liver	0.048 [0.024]	0.011–0.152	µg/g	
	Infants, postmortem (n=9)	Liver	0.0099 [0.007]	0.0034–0.019	µg/g	
	Adults, postmortem (n=8)	Lung	0.044 [0.022]	0.0121–0.125	µg/g	
	Infants, postmortem (n=9)	Lung	0.007 [0.0055]	0.0011–0.015	µg/g	
	Adults, postmortem (n=9)	Spleen	0.015 [0.008]	0.001–0.063	µg/g	
	Infants, postmortem (n=8)	Spleen	0.0049 [0.0045]	0.0011–0.0088	µg/g	

Table 5-6. Levels of Arsenic in Human Tissue and Urine—Recent Studies *(continued)*

Site	Population	Sample	Concentration			Reference
			Mean[a]	Range	Units	
Palatinate Region, Germany (high As)[2]	Residents (n=199)	Urine, 24-hour	3.96 [3.21]	<0.1–18.32	µg/g	Gebel et al. 1998a
	Residents (n=211)	Hair	0.028 [0.016]	<0.005–0.154	µg/g	
Saxony, Germany (low As - reference)	Residents (n=75)	Urine, 24-hour	7.58 [6.20]	0.29–23.78	µg/g	Gebel et al. 1998a
	Residents (n=74)	Hair	0.069 [0.053]	0.013–0.682	µg/g	
Ismir, Turkey, (volcanic area with high thermal activity)	Non-occupationally exposed women (n=35)	Breast milk	4.23 [4.26]	3.24–5.41	µg/L	Ulman et al. 1998
Erlangen-Nurenberg Germany 1/92–12/93	Non-occupationally exposed people (n=50)	Lung	5.5	<1–13.0	ng/g ww	Kraus et al. 2000
			28.4	<1–73.6	ng/g dw	

[a]Medians, if reported, are in brackets.
[B]Surprisingly, the reference group (Saxony) had significantly higher levels of arsenic in urine and hair. However, data from both groups correspond to normal range reference data.

dw = dry weight; ww = wet weight

Arsenic in soil in communities surrounding former smelters is a public health concern, especially for infants and children who may consume significant quantities of soil. Since lead arsenate was used in apple and other fruit orchards, often at very high application rates, and this compound would be expected to accumulate and persist in surface soil, there are concerns to human health when these when old orchards are converted into subdivisions or when they are used to grow food crops or forage. However arsenic in soil may be imbedded in minerals or occur as insoluble compounds such as sulfides and therefore not taken up by the body from the gastrointestinal tract. In addition, oxidation of mineral surfaces may result in armoring the primary mineral grain by a secondary reaction product. Arsenic-bearing solids are often encapsulated in insoluble matrices such as silica, further diminishing arsenic availability (Davis et al. 1992). In a study of the bioavailability of arsenic in soils from the Butte, Montana, mining district, Davis et al. (1992) prepared a soil that was representative of a mine waste site minimally impacted by smelting activity by blending five separate Butte soils to achieve an arsenic concentration of 13,800 µg/g. Based on *in vitro* results, the arsenic in the soil was demonstrated to be five times less bioavailable than arsenic from Na_2HAsO_4. The low bioavailability factors observed for arsenic-bearing soils from a former smelting site in Anaconda, Montana, were explained by the sparingly soluble nature of the arsenic-bearing phases, the presence of authigenic carbonate and silicate rinds, the kinetic hindrance to dissolution, and the inaccessibility of encapsulated arsenic (Davis et al. 1996). Data from another study of arsenic in soils and sediments at the Milltown Reservoir Sediments Superfund site in Montana indicated that the bioavailabilities of arsenic and other metals studied were equal to or less than 0.2% for internal organs and 0.1% for carcasses on a µg/g tissue wet weight basis. These results suggest that the bioavailable fraction of mining waste metals in riparian wetland soils may be quite small (Pascoe et al. 1994).

Hamel et al. (1998) used synthetic gastric juice to estimate the bioaccessible fraction of metals in the stomach with varying liquid to solid ratios. They found that the bioaccessibility may vary in different soils and with varying liquid to solid. Bioaccessibility was defined as the amount of metal that is soluble in synthetic gastric juice and therefore, potentially available for uptake across the intestinal lumen, while bioavailability was defined as the amount that was actually taken across the cell membranes. Arsenic bioaccessibility for National Institute of Standards and Technology (NIST) Montana Soil SRM 2710, with a certified arsenic concentration of 626 µg/g, was fairly consistent across the liquid-to-solid ratios and ranged from 41.8±18 to 56±21%. The extractability of a hazardous waste contaminated soil from Jersey City, New Jersey, was different than that observed for the Montana NIST soil. For the Jersey City soil, which had an arsenic concentration of 1,120 µg/g, there was an increase in the bioaccessible arsenic as the liquid-to-solid ratio increased. Bioaccessible arsenic ranged from 4.5±0.8 (at a liquid-to-solid ratio

of 100:1) to 25±9% (at a ratio of 5,000:1). Similarly, smelter impacted soils from Anaconda, Montana contain metal-arsenic oxides and phosphates whose bioaccessibility is limited by solubility restraints for residence times typical of the gastrointestinal tract (Davis et al. 1992, 1996).

Inhalation of arsenic from ambient air is usually a minor exposure route for the general population. For example, the dose to a person who breathes 20 m^3/day of air containing 20–30 ng/m^3 (see Section 5.4.1) would be about 0.4–0.6 µg/d. However, smokers may be exposed to arsenic by inhalation of mainstream smoke. Assuming that 20% of the arsenic in cigarettes is present in smoke, an individual smoking two packs of cigarettes per day would inhale about 12 µg of arsenic (EPA 1984a). However, a recent German study of the arsenic levels in lung tissue of 50 unexposed deceased people (see Table 5-6) found no significant difference in lung arsenic concentrations of smokers versus non-smokers, nor were there any significant age- or sex-related differences (Kraus et al. 2000). Before arsenical pesticides were banned, tobacco contained up to 52 µg As/g, whereas after the ban, maximum arsenic levels were reduced to 3 µg/g.

Occupational exposure to arsenic may be significant in several industries, mainly nonferrous smelting, arsenic production, wood preservation, glass manufacturing, and arsenical pesticide production and application. Since arsenic compounds are used as a desiccant for cotton, workers involved in harvesting and ginning cotton may be exposed to arsenic. Occupational exposure would be via inhalation and dermal contact. Should any arsenic be retained in the cotton, workers handling the fabric and the general public would be exposed. The electronics industry is expanding the use of gallium arsenide in the production of electro-optical devices and integrated circuits, and workers in the industry where gallium arsenide is used may be exposed to hazardous substances such as arsenic, arsine, and various acids (Sheehy and Jones 1993). Occupational exposure to arsenic is generally assessed by measuring urinary excretion of arsenic. Past exposure is commonly assessed by arsenic levels in hair. Different types of occupational exposures may result in different uptakes of arsenic because of the bioavailability of the form of arsenic to which workers are exposed. For example, maintenance workers at a Slovak coal-fired power plant exposed to 8-hour TWA arsenic air concentrations of 48.3 µg/m^3 (range, 0.17–375.2) had urinary total arsenic levels of 16.9 µg As/g creatinine (range, 2.6–50.8), suggesting that bioavailability of arsenic from airborne coal fly ash is about one-third that from in copper smelters and similar setting (Yager et al. 1997). Approximately 90% of the arsenic-containing particulates were $3.5 µm.

NIOSH researchers conducted a study of arsenic exposures and control systems for gallium arsenide operations at three microelectronics facilities during 1986–1987 (Sheehy and Jones 1993). Results at one

plant showed that in all processes evaluated but one, the average arsenic exposures were at or above the Occupational Safety and Health Administration (OSHA) action level of 5 μg/m^3, with a maximum exposure of 8.2 μg/m^3. While cleaning the liquid encapsulated Czochralski (LEC) pullers, the average potential arsenic exposure of the cleaning operators was 100 times the OSHA permissible exposure limit (PEL). Area arsenic samples collected at the plant in break-rooms and offices, 20–60 feet from the process rooms, had average arsenic concentrations of 1.4 μg/m^3. At the other two plants, personal exposures to arsenic were well controlled for all processes evaluated.

A study has been conducted to examine the relationship between total arsenic levels in hair of employees in a semiconductor fabrication facility and job responsibility, a surrogate variable for arsenic exposure (de Peyster and Silvers 1995). Airborne arsenic was found in areas where equipment was cleaned but not in administrative areas. The highest airborne arsenic level found in the study, 15 μg/m^3, was collected from the breathing zone of a maintenance employee who was cleaning a source housing over a period of 2 hours in an area with local exhaust ventilation. A concentration of 2 μg/m^3 was found during the remainder of the cleaning period (~53 minutes). Workers in maintenance who were regularly assigned to cleaning equipment, and therefore presumed to have the highest exposure potential, had a mean hair arsenic level of 0.042 μg/g. This was higher than the mean of 0.033 μg/g observed in administrative controls, but the difference was not significant. Maintenance workers who only occasionally cleaned and maintained arsenic-contaminated equipment had a mean hair arsenic level of 0.034 μg/g, which was comparable to the controls. The highest group mean hair arsenic level of 0.044 μg/g, surprisingly, was found in supervisors and engineers who were presumed to have the lowest exposure potential of all workers in the process areas. However, the highest concentrations of hair arsenic in engineers, 0.076 and 0.106 μg/g, were observed in 2 heavy smokers who smoked 1–2 packs of cigarettes per day. A 2-way analysis of variance indicated that smoking appeared to be a significant contributing factor whereas occupational exposure was not.

Chromium, copper, and arsenic (CCA) preservatives are commonly used for treating timber used in constructions in marine and other humid environments or in contact with the ground. Exposure to CCA compounds may occur through dermal contact and inhalation of dust while working with the treated timber. Nygren et al. (1992) investigated the occupational exposure to airborne dust, chromium, copper, and arsenic in six joinery shops in Sweden where impregnated wood was used for most of their production. The mean airborne concentration of arsenic around various types of joinery machines ranged from 0.54 to 3.1 μg/m^3. No increased concentrations of arsenic were found in the workers' urine. A study was carried out in Denmark to evaluate arsenic exposure in taxidermists, workers impregnating

wood with CCA solutions, fence builders, construction workers, and workers impregnating electric pylons with arsenic solution (Jensen and Olsen 1995). Airborne arsenic exposure was documented in 19 of 27 individuals working with products containing arsenic. The maximum exposure concentration was 17.3 μg/m^3, found for a single worker who was filling an impregnation container with CCA paste. Median exposures for indoor workers producing garden fences and weekend cottages were 3.7 and 0.9 μg/m^3, respectively. The maximum urine concentration reported in the study was 294.5 nanomoles arsenic per millimole creatinine (195 μgAs/g creatinine) and was from the injector impregnating electric pylons. The median concentration in workers on electric pylons was 80 nanomoles arsenic per millimole creatinine, which was 6 times the concentration in reference individuals. Urine arsenic levels in workers producing garden fences and in taxidermists were 2.9 and 1.8 times the reference level, respectively.

The NIOSH National Occupational Exposure Survey (NOES) conducted in 1981–1983 estimated that about 55,000 workers were potentially exposed to arsenic (NOES 1990). The NOES was based on field surveys of 4,490 facilities that included virtually all workplace environments, except mining and agriculture, where eight or more persons are employed. The principal exposure pathway is probably inhalation of arsenic adsorbed to particulates, but ingestion and possibly dermal exposure may also be common. Since arsenic is no longer produced in the United States (see Section 4.1) and many arsenical pesticide uses have recently been banned (see Chapter 7), it is likely that the number of workers occupationally exposed to arsenic has decreased markedly in recent years.

5.6 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 2.7 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).

As with adults, most children are exposed to arsenic largely through their diet. Since the greatest dietary intake of arsenic is from fish and seafood, infants and young children for whom a substantial part of their food is milk, would not be exposed to arsenic from dietary sources as much as older children. Even when mothers consumer large amounts of seafood, there does not appear to be any major transfer of arsenobetaine, the major form of arsenic in seafood, from seafood to milk (Grandjean et al. 1995). Arsenic concentrations were very low in human milk sampled from 88 mothers in the Faroe Islands, where the seafood diet includes pilot whale meat and blubber. The total arsenic concentrations ranged from 0.1 to 4.4 µg/kg, with a median of 1.6 µg/kg (Grandjean et al. 1995). The arsenic concentration in the breast milk of 35 women in Ismir, Turkey, a volcanic area with high thermal activity ranged from 3.24 to 5.41 µg/L, with a median of 4.22 µg/L (Ulman et al. 1998). The mean arsenic levels in three groups of cows in the region that grazed on land impacted by lava and thermal activity were 4.71, 4.46, and 4.93 µg/L, compared to 5.25 µg/L for cows kept in sheds and fed commercial pellet feed and municipal water. The urine of pregnant women and the cord blood of their infants were not very high, 0.625±0.027 and 0.825±0.079 µg/L, respectively. The authors concluded that there was no harmful exposure to arsenic in volcanic areas with high arsenic levels from suckling infants or feeding them local cow's milk, nor was there harm to the newborns from their mother's diet. According to the FDA study of 1986–1991, the mean daily intakes of arsenic are 0.5 and 0.81 µg/kg body weight per day for a 6–11-month-old infant and 2-year-old child, respectively (Gunderson 1995b). This can be compared to a mean daily intake of 0.51 µg/kg-body weight per day for a 25–30-year-old male (see Table 5-5). A more recent Total Diet Study, September 1991 to December 1996, estimated that the average inorganic arsenic intake for children of various age/sex groups were (age-sex group, total arsenic intake in µg/day, inorganic arsenic intake in µg/day): 6–11 months, 2.15, 1.35; 2 years, 23.4, 4.41; 6 years, 30.3, 4.64; 10 years, 13.3, 4.21; 14–16 years (females), 21.8, 5.15; 14–16 years (males), 15.4, 4.51 (Tao and Bolger 1999). The greatest dietary contribution (76–96%) of total arsenic intake for all age groups other than infants was seafood. For infants, 41 and 34% of the estimated total arsenic intakes are from seafood and rice/rice cereals, respectively (Tao and Bolger 1999). Only for toddlers does the intake approach the World Health Organization's (WHO) provisional tolerable daily intake (PTDI) for inorganic arsenic (see Table 5-5). Environment Canada (1993) estimated the daily intake of inorganic arsenic from food as <0.04–2.4, <0.05–2.0, <0.03–1.9, and <0.02–1.2 µg/kg body weight per day for 0–0.5, 0.5–4, 5–11, and 12–19-year-old children, respectively (see Table 5-4). A 1985–1988 Canadian total diet study estimated that 1–4-year-olds ingested 14.9 µg of total arsenic per day compared with 38.1 µg by the average Canadian and 59.2 µg for 20–39-year-old males (Dabeka et al. 1993).

Arsenic exposure from drinking water, while generally low compared with that from food, may be elevated especially in groundwater from areas where arsenic occurs naturally in soil such as the western and north central sections of the United States (see Table 5-2 and Figure 5-2). Environment Canada (1993) estimated arsenic intakes from drinking water for infants and children in the general population and those living near point sources (see Table 5-4). Intake from water in the unexposed population was 0.08 µg/kg body weight per day for infants 0–0.5 years old and 0.1–0.3 µg/kg body weight per day for older children. For those living near point sources, arsenic intake from water reached highs of 8.3 µg/kg body weight per day for infants 0–0.5 years old and 10–31 µg/kg body weight per day for older children. Exposure from air was much lower than from other sources even for those living in polluted areas (Environment Canada 1993).

Arsenic exposure in communities near mining and smelting facilities or where arsenic had formerly been applied to agricultural land are a public health concern, especially for infants and children. Since arsenic remains in the surface soil indefinitely and long past land uses may be forgotten, people may not realize that they are living in areas where high levels of arsenic may occur in soil. Contaminated soils pose a particular hazard to children because of both hand-to-mouth behavior and intentional ingestion of soil (pica) that contain metals and other contaminants (Hamel et al. 1998). In these communities, arsenic may contaminate carpeting or may have been tracked in from outside. Children may be exposed to this arsenic while crawling around or playing on contaminated carpeting. Exposure may also result from dermal contact with the soil, or by inhaling the dust and then swallowing it after mucociliary transport up out of the lungs. Because much of the arsenic in soil is embedded in or adsorbed to soil particles or insoluble, it may not be in a form accessible for uptake by the body. Environment Canada (1993) estimated arsenic intakes from soil and dirt for infants and children in the general population and those living near point sources (see Table 5-4). Intake from soil and dirt in the unexposed population was 0.03–0.08 µg/kg body weight per day for infants 0–0.5 years old and 0.02–0.05 µg/kg body weight per day for children 0.5–4 years old. For those living near point sources, arsenic intake from soil and reached highs of 3.0 µg/kg body weight per day for infants 0–0.5 years old and 1.9 µg/kg body weight per day for children 0.5–4 years old.

Hwang et al. (1997b) studied the arsenic exposure of children in Anaconda, Montana, in the vicinity of a former copper smelter from the summer of 1992 through the summer of 1993. Environmental samples and first morning voided urine samples from 414 children <72 months old were collected. Attention was focused on that fraction of the environmental source that was thought to be of the greatest risk to the child (i.e., arsenic in small particles [<250 µm]) that could most readily adhere to hands and toys and could be

inadvertently ingested. Average arsenic levels in different types of soil ranged from 121 to 236 µg/g. Several studies have reported mean soil ingestion values for children ranging from 9 to 1,834 mg/day. Assuming that high arsenic exposure areas have average arsenic levels in soil from 60–150 µg/g, the resulting daily arsenic intake from soil could range from 1 to 275 µg/day per child. The geometric mean of speciated urinary arsenic (combined As(III), As(V), monomethylarsonic acid, and dimethylarsinic acid) was 8.6±1.7 µg/L (n=289) in the Hwang study. The mean total urinary arsenic level was 19.1 µg/L, which was 11–22 µg lower than those reported in two previous studies in Anaconda (Baker et al. 1977; Hartwell et al. 1983) and only slightly higher the value of 17.7 µg/L that was found in a survey conducted in Anaconda in 1985, when the smelter had already been shut down (Binder et al. 1987). A nationwide survey on arsenic exposure in the vicinity of smelter sites revealed that children without excess arsenic exposure had average total urinary arsenic levels ranging from 5 to 10 µg/L (Hwang et al. 1997a). Compared to these values, the mean total urinary arsenic values found in the Hwang study were markedly higher, but they were still well below the WHO-recommended maximum excretion level for total arsenic of 100 µg/L as an action level for intervention. The investigators hypothesized that the relatively low urinary arsenic levels found in the study were probably a reflection of the low bioavailability of some forms of arsenic in contaminated soil. Hwang et al. (1997a) stated that arsenic intake through skin contact is insignificant and may be neglected in the assessment of childhood arsenic exposure. They recommend that parents or guardians pay more attention to their children's activity, especially hand-to-mouth behavior, even though the environmental contaminants might be elevated only slightly. Children in the northern Palatine region of German study, a former mining area characterized by high levels of arsenic (<2–605 µg/g) in residential areas did not show higher arsenic levels in their hair or urine than children from a reference area of Germany (Gebel et al. 1998a). No studies were found relating to prenatal exposure to arsenic (e.g., arsenic levels in amniotic fluid, cord blood).

Parents can inadvertently carry hazardous materials home from work on their clothes, skin, hair, tools, and in their vehicles (DHHS 1995). Falk et al. (1981b) reported a case of hepatic angiosarcoma in a child that could be associated with arsenic contamination of a parent's clothing, the water supply, and the environment. The father worked in a copper mine and smelter area where his clothing was contaminated with dust containing arsenic. His daughter, who exhibited a high degree of pica, ate dirt from the yard, and licked dirt off her father's shoes. In a study of arsenic levels in homes in Hawaii, Klemmer et al. (1975) found higher levels in homes of employees of firms that used arsenic for pesticides or wood preservation, compared to homes where residents' work did not involve arsenic. The concentration of arsenic in dust from the homes of workers exposed to arsenic ranged from 5.2 to 1080 µg/g, compared to concentrations of 1.1–31 µg/g in dust from control homes.

While the harmful effects of many components of tobacco smoke are well known, those due to heavy metals in the smoke have not been sufficiently emphasized. The adverse health effects of these toxic metals on the fetus through maternal smoking are of special concern (Chiba and Masironi 1992). The concentration of arsenic in tobacco is relatively low, usually below detectable limits (<1 µg/g). Although the concentrations of inorganic and organic arsenic in the urine of adults do not appear to be influenced by smoking, a positive association was found between urinary arsenic levels in children and parental smoking habits. As detailed in a WHO report, the mean arsenic level in the urine of children of nonsmoking parents was 4.2 µg/g creatinine, in children with one smoking parent, it was 5.5 µg/g, and in children with both parents smoking, it was 13 µg/g (Chiba and Maseroni 1992).

The use of Chinese herbal medicines (CHM) appears to be common among Chinese women. Both CHM and Chinese proprietary medicines (CPM) are used for treatment of minor ailments in babies and children. Herbal medicines are available in capsule or tablet form in drug stores, supermarkets, and by mail. The CPM "Sin Lak Pill," "Lu Shen Wan," and other anti-asthma preparations have been found to contain inorganic arsenic levels ranging from 25 to 107,000 µg/g, and cases of acute arsenic poisoning have been found in children and adults using these CPM (Chan 1994). Babies and children are particularly at risk because they may be given higher doses of these preparation per kg of body weight than adults would normally consume. They may also lack the hepatic enzymes responsible for drug biotransformation and detoxification (Chan 1994).

Various metallic pigments and colors in the form of salts or lakes are used in toy production. Therefore, children may be exposed to toxic metals while playing with toys, especially when they lick, suck, or swallow a toy or a piece of a toy. Toys produced in European Union Markets must conform to restrictions concerning the bioavailability of toxic metals, including arsenic. The maximum limit for bioavailability of arsenic from the accessible parts of a toy is set to 0.1 µg/day. This corresponds to an arsenic migration limit of 25 µg/g for all toy material, including modeling clay and paints (Rastogi and Pritzl 1996). A study was carried out to determine whether crayons, water colors, and water-based paints conform with the migration limits for toxic metals (Rastogi and Pritzl 1996). For the analysis, 94 samples representing 48 products were obtained from China, Taiwan, Japan, the United States, and European countries. Fifty-two samples showed migration of arsenic, ranging from 0.01 to 3.75 µg/g.

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

In addition to individuals who are occupationally exposed to arsenic (see Section 5.5), there are several groups within the general population that have potentially high exposures (higher than background levels) to arsenic. These populations include individuals living in proximity to sites where arsenic was produced, used (e.g., as a pesticide), or disposed, and individuals living near one of the 1,011 NPL hazardous waste sites where arsenic has been found at elevated levels in some environmental media (HazDat 2000). It also includes point sources such as smelters, coal-fired power plants, and municipal incinerators. People living in areas of volcanic activity may be exposed to higher levels of arsenic since high levels are more likely to be present in the environment. Other populations at risk of potentially high levels of exposure include those whose water supply contain high levels of arsenic and those consuming large amounts of seafood or seaweed. However, as pointed out previously (see Section 5.4.4), arsenic in seafood and seaweed is largely of the less harmful organic arsenicals. While elevated urinary arsenic excretion levels have been associated with the consumption of fish and seafood, in a recent study of 32 sport fish consumers from Lakes Erie, Huron, and Michigan, only 6 (19%) had detectable urine arsenic concentrations, >4 µg/L, and 5 of these consumed fish from Lake Huron (Anderson et al. 1998). Exposure of high levels of arsenic in drinking water is more apt to be absorbed by the body and be harmful than exposure to arsenic in seafood. For example, a group of 36 people in Zimapán, Mexico who consumed water from an aquifer with 1.0 mg As/L had hair arsenic levels of 2.6–14.1 µg/g (10 µg/g average), compared with 2.4–13.9 µg/g (6.19 µg/g average) for a reference population that consumed bottled water with less than 0.014 mg/L arsenic (Armienta et al. 1997).

A study was conducted to determine if significant arsenic exposure was occurring at a Superfund site in Fort Valley, Georgia (Hewitt et al. 1995). Random urine, 24-hour urine, hair, and fingernail samples were collected at the end of the workweek from 40 employees at an active pesticide manufacturing facility where arsenical pesticides had been produced for over 50 years prior to the mid-1970s. Measurement of arsenic in the urine is considered to be the best method for monitoring recent exposure in industrial populations. Hair and fingernail analyses may provide an indication of exposures that occurred up to several months prior to testing, but both can adsorb and strongly retain arsenic from external sources. Since arsenic is rapidly cleared from the blood (half-life of 3–4 hours), blood arsenic levels are not considered suitable for monitoring populations for chronic low-level arsenic exposure. Results of the Hewitt study are summarized in Table 5-6. Urinary arsenic levels for all workers were well within the commonly accepted normal range of <100 µg/L.

As noted above, workers in a number of industries may have high exposures to arsenic, especially if proper safety procedures are not followed. For members of the general population, above-average exposure to arsenic from drinking water is possible in areas of high natural arsenic levels in groundwater or elevated arsenic levels in drinking water due to industrial discharges, pesticide applications, or leaching from hazardous waste facilities. Individuals living in the vicinity of large smelters and other industrial emitters of arsenic may be exposed to above-average arsenic levels both in the air, and as a result of atmospheric deposition, in water and soil and subsequent uptake into crops.

People sawing or drilling arsenic-treated wood without protective masks or burning this wood may be exposed to elevated levels of arsenic in air.

Recreational and subsistence fishers that consume appreciably higher amounts of locally caught fish from contaminated bodies of water may be exposed to higher levels of arsenic associated with dietary intake. Arsenic contamination has triggered the issuance of several human health advisories (EPA 1998g). As of December 1997, arsenic was identified as the causative pollutant in a restricted consumption advisory for the general population for all fish in a 7-mile area including Devil's Swamp Lake and Bayou Baton Rouge in Louisiana. A commercial fish ban also was issued for crustaceans and crayfish in a 1,000-foot radius around the McCormack and Baxter wood treatment site in Portland, Oregon, and for crustaceans and bottom fish in Ostrich Bay, Washington. These advisories are active (see Figure 5-3).

5.8 ADEQUACY OF THE DATABASE

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

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.

Figure 5-3. Fish and Wildlife Advisories for Arsenic

Source: EPA 1998g

5.8.1 Identification of Data Needs

Physical and Chemical Properties. The chemical and physical properties of the arsenic species of chief toxicological and environmental concern are sufficiently well characterized to allow estimation of the environmental fates of these compounds. However, more information regarding the K_{ow} and K_{oc} values of the organic arsenicals would help predict the fate of these compounds in the environment.

Production, Import/Export, Use, and Release and Disposal. While arsenic has not been produced in the United States since 1985, the United States is the largest consumer of arsenic and substantial quantities of arsenic are imported, primarily as arsenic trioxide (USGS 1998a). The agricultural use of inorganic arsenic pesticides have been discontinued in the United States. However, some organic arsenicals still may be used in agriculture. Current production and use data for individual arsenical pesticides and other arsenic compounds would help to estimate human exposure to the various arsenic species. Because arsenical pesticides are so persistent, a more complete picture of past use of these products would enable us to predict what areas may contain high levels of arsenic in soil.

Comprehensive estimates on emissions of arsenic date to the early 1980s (Nriagu and Pacyna 1988). The industrial picture has changed considerably since then and emission controls are being mandated more and more. For example, emission factors for Canadian smelters calculated in 1993 were grossly lower than those estimated in 1983 (Skeaff and Dubreuil 1997). There is a need for accurate and up-to-date measurements of atmospheric arsenic releases from both natural and anthropogenic sources to better assess human exposure to arsenic and guide environmental protection measures.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1997, became available in 1999. This database is updated yearly and provides a listing of facilities that produce, process, or use substantial quantities of arsenic and its compounds and their emissions. As of January 1, 1998 several industries that had been excluded from the TRI will be required to report. These include several industrial sectors that may have substantial arsenic emissions, such as metal mining, coal mining, electric utilities, and commercial hazardous waste treatment facilities. This will give us more completely emissions data for making exposure estimates.

Environmental Fate. The interconversion of the various arsenic species and transport among the environmental media is complex and not all aspects are well-studied. Additional quantitative data on the rates of oxidation, reduction, and biotransformation reactions of arsenic compounds, and how these depend on environmental conditions would be useful in evaluating and predicting the fate and transport of arsenic at hazardous waste sites and other areas.

Bioavailability from Environmental Media. Toxicokinetic and toxicity studies establish that bioaccessible (e.g., soluble, not strongly adsorbed to soil or embedded in minerals) arsenic is highly absorbed following inhalation and oral exposure (see Sections 2.3.1.2 and 2.3.1.1). Some work has been done on the effect of environmental matrix (soil, food) on accessibility and absorption of arsenic (Davis et al. 1992, 1996; Hamel et al. 1998), but additional data would be valuable. Limited data suggests that dermal absorption of arsenic is very low (see Section 2.3.1.2), further data would be useful to establish whether arsenic uptake occurs from contact with contaminated soil or water, since humans may be exposed by these routes near hazardous waste sites.

Food Chain Bioaccumulation. Bioconcentration factors have been measured for several freshwater and marine species. While some species (mainly marine algae and shellfish) tend to bioconcentrate arsenic (EPA 1980a; Roper et al. 1996), it is not biomagnified through the food chain (Eisler 1994; EPA 1979, 1982b, 1983e). In addition, arsenic in marine biota primarily occurs as arsenobetaine which poses little risk for consumers (Eisler 1994). Carrots growing on land containing somewhat more than the permissible of arsenic in crop land did not contain levels of arsenic that were harmful (Helgesen and Larsen 1998). However, further research on the uptake of arsenic by a variety of plants in a wide range of arsenic polluted sites (e.g., mining area, orchards previously treated with lead arsenate) would be valuable in assessing human exposure near such sites through the consumption of vegetables from home gardens.

Exposure Levels in Environmental Media. Extensive monitoring data are available for total arsenic in all environmental media. However, few studies have monitored individual arsenic species in air, water, soil, and biological matrices. Additional monitoring studies that include identification of arsenic species would allow more precise estimation of current exposure levels and possible human health risks.

Reliable monitoring data for the levels of arsenic in contaminated media at hazardous waste sites are needed so that the information obtained on levels of arsenic in the environment can be used in

combination with the known body burdens of arsenic to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. Arsenic has been detected in human tissues, including blood, urine, hair, nails, and internal organs. Data are available for populations exposed in the workplace and for the general population (de Peyster and Silvers 1995; Jensen and Olsen 1995; Nygren et al. 1992), and some studies have been published on exposures near waste sites (Davis et al. 1992, 1996; Hwang et al. 1997a). Additional biomonitoring studies of residents near waste sites that contain arsenic would be helpful in evaluating the likely human health risks from these sites. This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Contaminated soils pose a particular hazard to children because of pica and hand-to-mouth activities. Some studies have been performed on exposure and body burden (Hamel et al. 1998; Hwang et al. 1997a), but additional studies, including investigations of unique pathways for exposures of children and the amount of soil a child ingests, would provide valuable data. The PTDI assigned by the FAO/WHO applies to adults. Studies are needed to assess whether children are different in their weight adjusted intake of arsenic. No childhood specific means for reducing exposure were identified.

Child health data needs relating to susceptibility are discussed in Section 2.1.2.2 Identification of Data Needs: Children's Susceptibility.

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

5.8.2 Ongoing Studies

The Federal Research in Progress (FEDRIP 1998) database provides additional information obtainable from a few ongoing studies that may fill in some of the data needs identified in Section 5.8.1. These studies are summarized in Table 5-7.

Table 5-7. Ongoing Studies on Arsenic

Investigator	Affiliation	Research description	Sponsor
Amrhein, C	University of California Soil and Environmental Science, Riverside, California	Biogeochemistry and management of salts and possible toxic trace elements in arid soils, sediments, and waters	USDA Cooperative State Research Service
Basta, N	Oklahoma State University, Agronomy Stillwater, Oklahoma	Chemistry and bioavailability of waste constituents in soils	USDA Cooperative State Research Service
Barbarick, KA	Colorado State University, Agronomy, Fort Collins, Colorado	Chemistry and bioavailability of waste constituents in soils	USDA Cooperative State Research Service
Barton, Larry	University of New Mexico, Albuquerque, New Mexico	Mechanisms of metal transformation in bacteria	National Institute of General Medical Sciences
Belitz, Kenneth	Dartmouth College Hanover, New Hampshire	Subsurface transport and fate of cadmium, arsenic, and lead	NIEHS
Chaney, Rufus L	Beltsville Agricultural Research Center, Beltsville, Maryland	Comparison of *in situ* remediation of contaminated soils, water, and air using composts	USDA Cooperative State Research Service
Chang, AC; Page, AL; Amrhein, C	University of California, Soil and Environmental Science, Riverside, California	Chemistry and bioavailability of waste constituents in soils	USDA Cooperative State Research Service
Doner, HE	University of California, Environmental Science, Policy, and Management, Berkeley, California	The role of the solid phase in controlling the distribution of selected trace elements in soils	USDA Cooperative State Research Service
Doner , H; Amundson, R	University of California, Soil Science, Berkeley, California	Biogeochemistry and management of salts and potentially toxic trace elements in arid-zone soils, sediments	USDA Cooperative State Research Service
Dudley, LM; Grossl , P; Boettinger, JL	Utah State University, Plants, Soils, and Biometeorology, Logan, Utah	Biogeochemistry and management of salts and potentially toxic elements in arid-zone soils sediments	USDA Cooperative State Research Service
Fendorf, SE	Univ of Idaho, Plant, Soil, and Entomological Science, Moscow, Idaho	Stability and fate arsenate compounds subjected to reducing soil conditions	USDA Competitive Research Grant Office

Table 5-7. Ongoing Studies on Arsenic *(continued)*

Investigator	Affiliation	Research description	Sponsor
Friedland, Andrew J	Dartmouth College, Hanover, New Hampshire	Sources and mobility of lead and cadmium in soil, groundwater, and vegetation	NIEHS
Gordon, Terry	New York University, Tuxedo, New York	Bioavailablility of heavy metals in pressure treated wood	NIEHS
Hamilton, Joshua W	Dartmouth College, Hanover, New Hampshire	Toxic metals—biological and environmental implications	NIEHS
Hemond, Harold F	Massachusetts Institute of Technology, Cambridge, Massachusetts	Chemical transport and human exposure on the Aberjona watershed	NIEHS
Hyatt, DE	Chemical and Metal Industries, Denver, Colorado	Recovery of arsenic, antimony, chlorocarbons from spent fluorocarbon catalyst	Not stated
Inskeep, WP	Montana State University, Plant and Soil Sciences, Bozeman, Montana	Biogeochemistry and management of salts and protein toxic trace elements in arid-zone soils, sediments, and waters	USDA Cooperative State Research Service
Inskeep, WP	Montana State University, Plant and Soil Sciences Bozeman, Montana	Fate and transport of chemicals in soils	USDA Cooperative State Research Service
Integrated Laboratory Systems, Inc.	Arsenic Research Partnership	Sodium arsenite in drinking water, bladder, and skin tumor studies in heterozygous p53 deficient mice.	USEPA
Logan, TJ Traina, SJ	Ohio State University, Horticulture and Crop Science, Columbus, Ohio	Chemistry and bioavailability of waste constituents in soils	USDA Cooperative State Research Service
Manning, B Amrhein, C	University of California, Soil and Environmental Science, Riverside, California	Transformation and transport of arsenic (III) and arsenic (V) in soil columns	USDA Competitive Research Grant Office
Naylor, DV	Univ of Idaho, plant Soil and Entomological Science, Moscow, Idaho	Arsenic and phosphorus interaction with soils subjected to flooding and drainage	USDA Cooperative State Research Service
Nepf, H	Massachusetts Institute of Technology, Cambridge, Massachusetts	Hydrodynamic controls on metal remobilization from sediments of the Mystic Lakes	NIEHS

Table 5-7. Ongoing Studies on Arsenic *(continued)*

Investigator	Affiliation	Research description	Sponsor
Odom, JW	Auburn University, Agronomy and Soils, Auburn, Alabama	Occurrence, accumulation, and plant availability of boron, copper, sulfur, and heavy metals in acid ultiso	USDA Cooperative State Research Service
Peryea, FJ	Washington State University, Agronomy and Soils, Pullman, Washington	Biogeochemistry and management of salts and potentially toxic trace elements in arid-zone soils, sed	USDA Cooperative State Research Service
Pigeaud, A	Energy Research Corporation, Danbury, Connecticut	Trace element emissions	USDOE
Not stated	Research Triangle Institute, Arsenic Research Partnership	Analytical methods for determining arsenic contribution from dietary sources	USEPA
Silver, S	University of Illinois at Chicago, Department of Microbiology and Immunology, Chicago, Illinois	Oxidation and reduction of arsenic oxyanions: a molecular genetics, bio-chemistry, and micro-biological approach	Not stated
Smith, AH	University of California, Berkeley	Dose-response susceptibility investigation of skin keratoses and hyperpigmentation due to ingestion of arsenic in drinking water	USEPA
Snow, ET	New York University Medical Center	Arsenic-glutathione interactions and skin cancer	USEPA
Styblo, M	University of North Carolina at Chapel Hill, University of British Columbia, Vancouver	Mode of action of inorganic arsenic as a carcinogen and toxin including glutathione reductase and cellular redox status	USEPA
Suarez, Donald L	Agricultural Research Service, Riverside, California	Management of saline and sodic soils	USDA Agricultural Research Service
Tabatabai, MA	Iowa State University, Agronomy, Ames, Iowa	Chemistry and bioavailability of waste constituents in soils	USDA Cooperative State Research Service

Table 5-7. Ongoing Studies on Arsenic *(continued)*

Investigator	Affiliation	Research description	Sponsor
Torrents, Alba; Davis, Allen P	University of Maryland College Park, Department of Civil Engineering, College Park, Maryland	A joint research effort between UMCP and UNAM	National Science Foundation, Division of Bioengineering and Environmental Systems
Vance; GF	University of Wyoming, Plant, Soil, and Insect Science, Laramie, Wyoming	Chemistry and bioavailability of waste constituents in soils	USDA Cooperative State Research Service
Not specified	TD Research Inc., Wheat Ridge, Colorado	A novel extractant for the selective removal of arsenic from industrial waste waters	Not stated
Not specified	University of Alberta, University of British Columbia	Analytical detection of arsenic in biological matrices	Not stated
Not specified	University of Alberta, University of Michigan	Arsenic effect on gene expressions and its relationship to cancer	Not stated
Not specified	University of California, Berkeley	Feasibility of new epidemiologic studies of low level arsenic in drinking water	Not stated
Not specified	To be determined	Arsenic human health effects: cancer/noncancer epidemiological study	Not stated

NIEHS = National Institute of Environmental Health Sciences; USDA = U.S. Department of Agriculture; USDOE = U.S. Department of Energy

6. ANALYTICAL METHODS

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

6.1 BIOLOGICAL MATERIALS

Atomic absorption spectrophotometry (AAS) is the most common analytical procedure for measuring arsenic in biological materials (Curatola et al. 1978; Foa et al. 1984; Johnson and Farmer 1989; Mushak et al. 1977; Norin and Vahter 1981; Sotera et al. 1988). In AAS analysis, the sample is heated in a flame or in a graphite furnace until the element atomizes. The ground-state atomic vapor absorbs monochromatic radiation from a source and a photoelectric detector measures the intensity of transmitted radiation (APHA 1989b). Inductively-coupled plasma atomic emission spectrometry (ICP-AES) and ICP-mass spectrometry (ICP-MS) are increasingly common techniques for the analysis of arsenic; both methods can generally provide lower detection limits than absorbance detection methods.

Samples may be prepared for AAS in a variety of ways. Most often, the gaseous hydride procedure is employed (Curatola et al. 1978; Foa et al. 1984; Johnson and Farmer 1989; Norin and Vahter 1981). In this procedure, arsenic in the sample is reduced to arsine (AsH_3), a gas which is then trapped and introduced into the flame. This approach measures total inorganic arsenic, but may not detect all organic forms unless preceded by a digestion step. Digestion or wet-ashing with nitric, sulfuric and/or perchloric acids degrades the organic arsenic species to inorganic arsenic so that recovery of total arsenic from biological materials can be achieved (Maher 1989; Mushak et al. 1977; Versieck et al. 1983). For accurate results, it is important to check the completeness of the oxidation, however, this is seldom done (WHO 1981).

The arsenic concentration in biological fluids and tissues may also be determined by neutron activation analysis (NAA) (Landsberger and Simsons 1987; Versieck et al. 1983). In this approach, the sample is irradiated with a source of neutrons which converts a portion of the arsenic atoms to radioactive isotopes which can be quantified after separation from radioisotopes of other chemicals. Neutron activation has limited use because of the limited number of nuclear reactors in the United States providing this service and the need to dispose of radioactive waste. X-ray fluorescence is also capable of measuring arsenic in biological materials (Bloch and Shapiro 1986; Clyne et al. 1989; Nielson and Sanders 1983) and environmental samples (see Section 6.2). This method has the advantage that no sample digestion or separation steps are required. Hydride generation combined with atomic fluorescence spectroscopy (HG/AFS) is a relatively new technique that provides freedom from interference offered by hydride generation with sensitivity better than to 20 parts per trillion and linearity up to 10 ppm (PSA 2000).

Speciation of arsenic (i.e., analysis of organo-arsenicals or different inorganic species, rather than total arsenic) is usually accomplished by employing separation procedures prior to introduction of the sample material into a detection system. Various types of chromatography or chelation-extraction techniques are most commonly used in combination with AAS, ICP-AES, or ICP-MS detection methods (Dix et al. 1987; Foa et al. 1984; Johnson and Farmer 1989; Mushak et al. 1977; Norin et al. 1987; Thomas and Sniatecki 1995). In one method, HPLC is combined with HG/AFS to quantify As(III), dimethylarsinic acid (DMA), momomethyl arsonic acid (MMA), and As(V) (PSA 2000). Another approach involves selective reduction of arsenate and arsenite (permitting quantification of individual inorganic arsenic species), and selective distillation of methyl arsines to quantify MMA and DMA (Andreae 1977; Braman et al. 1977; Crecelius 1978). Most methods for measuring arsenic in biological samples, are unable to measure arsenobetaine with any accuracy because it does not form a hydride and it gives a different response from inorganic arsenic in electrothermal AAS. Ebdon et al. (1999) successfully employed using high performance liquid chromatography (HPLC) coupled with ICP-MS to determine arsenic speciation in blood plasma which was entirely ansenobetaine. Since marine foods are largely organic arsenic while inorganic arsenic compounds, being the most toxic forms of arsenic and therefore of highest concern, Øygard et al. (1999) developed a simple method to determine inorganic arsenic in biological samples. Their method, that involves initially distilling inorganic arsenic from the sample as $AsCl_3$ using HCl, avoids separating and quantifying all the different arsenic species which is both costly and time-consuming.

Table 6-1 summarizes a variety of methods for measuring total arsenic and individual arsenic species in biological materials. None of these methods have been standardized by EPA or other federal agencies.

Table 6-1. Analytical Methods for Determining Arsenic in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Methods for total arsenic:					
Blood	Digestion with nitric acid and hydrogen peroxide; dry ash with magnesium oxide/magnesium nitrate; reduction with sodium borohydride	HGAAS	0.5 µg/L	95–102	Foa et al. 1984
Blood, hair	Wet ash with nitric/perchloric acids; reduction with sodium borohydride	HGAAS	0.1 µg/L[a]	95–105	Valentine et al. 1979
Serum	Irradiation; digestion with nitric/perchloric/sulfuric acids; extraction with toluene	NAA	0.088 ng/mL[a]	94–98	Versieck et al. 1983
Urine	Irradiate epithermally	NAA	40–100 ng/g	93–109	Landsberger and Simsons 1987
Urine	Digestion with nitric and perchloric acid; reduction with tin chloride; generation arsine by addition of zinc; reaction with SDDC	Colorimetric photometry	0.5 µg/sample	90–110	Pinto et al. 1976
Urine	Pre-treatment with L-cysteine; reduction with potassium iodide/ascorbic acid	Flow injection HGAAS	0.1 µg/L	95–100	Guo et al. 1997
Urine	Drying sample; irradiation with x-rays	XRF	0.2 µg/L[a]	92–108	Clyne et al. 1989
Hair	Wet ashing with nitric/sulfuric acids and hydrogen peroxide; reduction to arsine with sodium borohydride	HGAAS	0.06 µg/g	93	Curatola et al. 1978
Soft tissue	Digestion with nitric/sulfuric acids; complexation with DDDC in potassium iodide; extraction with chloroform	GFAAS	0.2 ppm	79.8	Mushak et al. 1977

Table 6-1. Analytical Methods for Determining Arsenic in Biological Samples *(continued)*

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Nails	Wet ashing with nitric/sulfuric acids and hydrogen peroxide; reduction to arsine with sodium borohydride	HGAAS	1.5 µg/g	No data	Agahian et al. 1990
Methods for arsenic speciation:					
Urine	Separation of As^{+3}, As^{+5}, MMA, and DMA on anion/cation exchange resin column; reduction to respective arsines with sodium borohydride	IEC/HGAAS	0.5 µg/L	93–106	Johnson and Farmer 1989
Urine	Reduction of As^{+3}, As^{+5}, MMA, and DMA to arsines with sodium borohydride	HGAAS	0.08 µg/L	97–104	Norin and Vahter 1981
Urine	Reduction of As^{+3}, As^{+5}, MMA, and DMA to arsines; collection in cold trap; selective distillation by slow warming	Atomic emission (direct-current plasma)	#1 ng for all four species	No data	Braman et al. 1977
Urine	Extraction with chloroform/methanol; column separation with chloroform/ methanol; elution on cation exchange column with ammonium hydroxide	HGAAS/TLC/ HRMS	0.34 mg/ sample[a]	No data	Tam et al. 1982
Blood/tissue	Acidification with hydrochloric acid; complexation with TGM; extraction into cyclohexane; separation on capillary column	GLC/ECD	0.1 mg/mL	No data	Dix et al. 1987
Blood plasma	Separation by HPLC	HPLC/ICP-MS	2.5 ng As/mL	~100	Ebdon et al. 1999
Urine	Separation by anion exchange chromatography; detection by direct coupling of column to ICP-MS	IEC/ICP-MS	<0.45 µg/L for all species	No data	Inoue et al. 1994

Table 6-1. Analytical Methods for Determining Arsenic in Biological Samples *(continued)*

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Marine biota	Extraction with methanol-water; removal of fats by liquid-liquid extraction or solid-phase cartridge	HPLC/ICP-MS	6–25 ng/mL	94.6 (fish muscle CRM)	Sniatecki 1994
Marine biota	Separation by anion exchange coupled with HPLC; on-line microwave oxidation	HPLC/HGAAS	0.3–0.9 ng	95–110 (recovery of spike in fish tissue)	López-Gonzálvez et al. 1994
Biological samples - Inorganic arsenic	Distill inorganic arsenic as $AsCl_3$ using HCl after pre-reduction of As(V) with KI/HCl	Flow-injection HGAAS	0.045 mg/kg (dry matter)	No data	Øygard et al. 1999

[a] Lowest reported concentration

CRM = certified reference material; DDDC = diethylammonium diethyldithiocarbamate; DMA = dimethylarsinate; ECD = electron capture detector; GFAAS = graphite furnace atomic absorption spectrometry; GLC = gas-liquid chromatography; HGAAS = hydride generation atomic absorption spectrometry; HRMS = high resolution mass spectrometry; ICP-MS = inductively-coupled plasma mass spectrometry; IEC = ion exchange chromatography; HPLC = high-performance liquid chromatography; MMA = monomethylarsonate; NAA = neutron activation analysis; SDDC = silver diethyldithiocarbamate; TGM = thioglycolic acid methylester; TLC = thin layer chromatography; XRF = x-ray fluorescence

Detection limits in blood and urine are about 0.1–1 ppb for most techniques; limits for hair and tissues are usually somewhat higher.

6.2 ENVIRONMENTAL SAMPLES

Arsenic in environmental samples is also measured most often by AAS techniques, with samples prepared by digestion with nitric, sulfuric and/or perchloric acids (Dabeka and Lacroix 1987; EPA 1983b, 1994a, 1994b; Hershey et al. 1988). Other methods employed include a spectrophotometric technique in which a soluble red complex of arsine and silver diethyldithiocarbamate (SDDC) is formed (APHA 1977; EPA 1983c), ICP-AES (EPA 1982b, 1996a), graphite furnace AAS (EPA 1994b), ICP-MS (EPA 1998j), and X-ray fluorescence (Khan et al. 1989; Nielson and Sanders 1983).

Since arsenic in air is usually associated with particulate matter, standard methods involve collection of air samples on glass fiber or membrane filters, acid extraction of the filters, arsine generation and analysis by SDDC spectrophotometry or AAS (APHA 1977; NIOSH 1984).

Methods standardized by the EPA for measuring total arsenic in water and wastewater, solid wastes, soil and sediments include: ICP-MS (EPA 1998j, 1994a, 1991), ICP-AES (EPA 1996d), graphite furnace AAS (EPA 1994b), quartz furnace hydride generation AAS (EPA 1996h) and an electrochemical method using anodic stripping voltammetry (ASV) (EPA 1996e). A modification using cryogenic GC to EPA Method 1632 (HG/AAS) allows the technique to be adopted for the species As(III), As(V), MMA, and DMA to the 0.003 ppb level (1996f). Similar methods are recommended by APHA for water using AAS/hydride generation (APHA 1989c), AAS/graphite furnace technique (APHA 1989b), ICP (APHA 1989d), or SDDC spectrophotometry (APHA 1989a). The AAS/hydride generation method is generally resistant to matrix and chemical interferences (APHA 1989a). Techniques to compensate for these interferences have been described by EPA (1982b).

Analysis for arsenic in foods is also most frequently accomplished by AAS techniques (Arenas et al. 1988; Dabeka and Lacroix 1987; Hershey et al. 1988; Tam and Lacroix 1982). Hydride generation is the sample preparation method most often employed (Arenas et al. 1988; Hershey et al. 1988), but interferences must be evaluated and minimized.

Speciation of inorganic arsenic in environmental samples is usually accomplished by chromatographic separation, chelation-extraction or elution of As^{+3} and then reduction of As^{+5} with subsequent similar

treatment (Butler 1988; López-Gonzálvez et al. 1994; Mok et al. 1988; Rabano et al. 1989). Methods are also available for quantifying organic arsenicals in environmental media, including arsenobetaine in fish (Beauchemin et al. 1988; Cannon et al. 1983) and other organic forms of arsenic in water, soil, and foods using hyphenated methods of separation and detection (HPLC/ICP-MS, HPLC/HGAAS, IC/ICP-MS) (Andreae 1977; Braman et al. 1977; Comber and Howard 1989; Crecelius 1978; Heitkemper et al. 1994; López-Gonzálvez et al. 1994; Odanaka et al. 1983; Teräsahde et al. 1996).

A summary of selected methods for analysis of total arsenic and individual inorganic and organic arsenic species in environmental samples is presented in Table 6-2.

6.3 ADEQUACY OF THE DATABASE

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

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

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. The most useful biomarkers of exposure to arsenic are levels of arsenic in urine, hair, or nails. Existing methods are sufficiently sensitive to measure background levels of arsenic in these tissues for average persons, and to detect increases as a result of above-average exposure (Agahian et al. 1990; Curatola et al. 1978; Clyne et al. 1989; Foa et al. 1984; Gebel et al. 1998b; Landsberger and Simsons 1987; Mushak et al. 1977; Pinto et al. 1976; Valentine et al. 1979; Versieck et al. 1983). The precision and accuracy of these methods are documented. Methods are also available that can distinguish nontoxic forms of arsenic (arsenobetaine)

Table 6-2. Analytical Methods for Determining Arsenic in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Methods for total arsenic:					
Air (particulates)	Collection on cellulose ester membrane filter; digestion with nitric acid, sulfuric acid, and perchloric acid	NIOSH Method 7900; HGAAS	0.02/sample	No data	NIOSH 1994
Air (particulate arsenic and arsenic trioxide vapor)	Collection on Na_2CO_3-impregnated cellulose ester membrane filter and H_2O_2	NIOSH Method 7901; GFAAS	0.06/sample	No data	NIOSH 1994
Air	Collection on cellulose ester membrane filter; digestion with nitric acid, sulfuric acid, and perchloric acid	NIOSH Method 7300; ICP-AES	0.001 µg/m^3	No data	NIOSH 1994
Water/waste water	Digestion with nitric acid	EPA Methods 200.7 and 6010B; ICP-AES	35 µg/L	86–105	EMMI 1997; EPA 1982c, 1996d
Water/soil/solid waste	Digestion with nitric acid and hydrogen peroxide	EPA Methods 206.2 and 7060A; GFAAS with $Ni(NO_3)_2$ modifier	1 µg/L	85–106	EPA 1983b, 1994b
Water/waste water/ solid waste	Digestion with nitric acid	EPA Methods 200.8, 6020 and 6020A; ICP-MS	0.4 µg/L	97–114	EMMI 1997; EPA 1991, 1994a, 1998j
Water/soil/solid waste	Digestion with nitric/sulfuric acid; reduction to As^{+3} with tin chloride; reduction to arsine with zinc in acid solution	EPA Methods 206.3 and 7061; HGAAS	2 µg/L	85–94	EPA 1983c, 1986d

Table 6-2. Analytical Methods for Determining Arsenic in Environmental Samples *(continued)*

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water	Reduction to arsine in acid solution; reaction with SDDC	EPA Method 206.4; SDDC colorimetric spectrophotometry at 510 nm	10 µg/L	100	EPA 1983d
Water	Digestion with 6M HCl; reduction to arsine wth sodium borohydride; cold trap and desorption into quartz furnace	EPA Method 1632; HGAAS	2 ng/L	No data	EMMI 1997; EPA 1996h
Food	Digestion with nitric acid; dry ashing with magnesium oxide; reduction with ascorbic acid; precipitation with APDC in presence of nickel carrier	GFAAS	10 ng	86–107	Dabeka and Lacroix 1987
Food	Digestion with nitric/sulfuric/perchloric acids; reduction to trivalent arsenic with potassium iodide; reduction to arsine with sodium borohydride	HGAAS	0.1 µg/g	98–110	Hershey et al. 1988
Soil, rock, coal	Preparation of pellet	XRF (backscatter)	4 mg/kg	SRM recoveries: 110±4 in soil; 100±1in rock; 97±18 in coal	Nielson and Sanders 1983
Methods for species of arsenic:					
Air (particulate organoarsenals)	Collection on PTFE filter	NIOSH Method 5022; ion chromatography/ HGAAS	0.2 µg As/sample	No data	NIOSH 1994

Table 6-2. Analytical Methods for Determining Arsenic in Environmental Samples *(continued)*

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air particulates (As^{+3} and As^{+5} only)	Collection on PFTE filter in high volume dichotomous virtual impactor; desorption with ethanolic hydrochloric acid; selective reduction of As^{+3} to arsine with zinc in acid and reduction of As^{+5} to arsine with sodium tetrahydrodiborate	HGAAS	1 ng/m^3	95±7 (As^{+3}) 100±8 (As^{+5}) on spiked materials	Rabano et al. 1989
Water	Selective elution of As^{+3} with orthophosphoric acid; elution and conversion of As^{+5} to As^{+3} with sulfur dioxide	IEC/amperometric detector (detects As^{+3} only)	0.9 µg/L	95% of converted As^{+5} recovered	Butler 1988
Water/soil	Selective complexation of As^{+5} with ammonium molybdate; extraction with isoamyl alcohol to separate from As^{+3}	Colorimetric spectrometry at 712 nm	No data	No data	Brown and Button 1979
Water	Selective extraction extraction of As^{+3} with APDC into chloroform; back extraction with nitric acid; reduction of As^{+5} to As^{+3} with thiosulfate and extract	NAA	0.01 ppb	No data	Braman et al. 1977
Food (arsenobetaine in fish)	Extraction of arsenobetaine with methanol/chloroform; digestion with nitric acid/magnesium nitrate for remainder of As species	HPLC/ICP-MS	0.3 ng as arsenobetaine	101±4 recovery of arsenobetaine	Beauchemin et al. 1988
Water/waste water/soil (inorganic species)	Acidification or digestion with hydrochlroic acid	EPA Method 7063; ASV	0.1 µg/L	96–102	EPA 1996e

Table 6-2. Analytical Methods for Determining Arsenic in Environmental Samples *(continued)*

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water	Cryogenic GC, Digestion with 6M HCl; reduction to arsine wth sodium borohydride; cold trap and desorption into quartz furnace	EPA Method 1632 appendix; HGAAS	3 ng/L	No data	EPA 1996h
Water	Reduction to arsines; cold trap and selectively warm to separate arsine species	AAS	2 ng/L	91–109	Andreae 1977
Water	Reduction of MMA, DMA and inorganic As (control pH to select As^{+3} or As^{+5}) to arsines with sodium tetrahydroborate; cold trap and selectively warm to separate arsine species	HGAAS	0.019–0.061 ng	No data	Comber and Howard 1989
Water/soil	Extraction with sodium bicarbonate; reduction of inorganic arsenic, MMA and DMA to hydrides with sodium borohydride; cold trap arsines in *n*-heptane	HG-HCT/GC-MID	0.2–0.4 µg/L	97–102	Odanaka et al. 1983

AAS = atomic absorption spectrophotometry; APDC = ammonium pyrrolidine dithiocarbamate; ASV = anodic stripping voltammetry; DMA = dimethylarsinate; EPA = Environmental Protection Agency; GC-MID = gas chromatography-multiple ion detection; GFAAS = graphite furnace atomic absorption spectrometry; HGAAS=hydride generation-atomic absorption spectroscopy; HG-HCT = hydride generation-heptane cold trap; HPLC = high perpformance liquid chromatography; ICP-AES = inductively coupled plasma-atomic emission spectrometry; ICP-MS = inductively coupled plasma-mass spectrometry; IEC = ion exchange chromatography; MMA = monomethylarsonate; NAA = neutron activation analysis; NIOSH = National Institute of Occupational Safety and Health; PTFE = polytetrafluoroethylene; SDDC = silver diethyldithiocarbamate; SRM = standard reference material; XRF = X-ray fluorescence

from inorganic and organic derivatives that are of health concern (Braman et al. 1977; Dix et al. 1987; Johnson and Farmer 1989; Norin and Vahter 1981; Tam et al. 1982). Further efforts to improve accuracy, reduce interferences and detect multiple species using a single analysis would be valuable.

Arsenic is believed to act by inhibition of numerous cell enzymes and/or by interfering with phosphate metabolism, and effects on several enzyme systems have been characterized in animals and *in vitro*. However, these effects are not specific to arsenic, and most can only be measured in tissue extracts. Efforts to identify an arsenic-specific enzymic or metabolic effect would be valuable, particularly if the effect could be measured using non-invasive techniques, and if the effect were specifically linked to the dermal, neurological, or hematological injuries that are characteristic of arsenic toxicity.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Arsenic is ubiquitous in the environment. It is found in air, water, soil, sediments, and food in several inorganic and organic forms. Analytical methods exist for the analysis of arsenic species in all of these environmental media, and these methods have the sensitivity to measure background levels and to detect elevated concentrations due to emissions from sources such as smelters, chemical plants, or hazardous waste sites (APHA 1977, 1989c; EPA 1982b, 1983a, 1983b, 1983c, 1991, 1994b, 1996a, 1996f). However, further research to reduce chemical and matrix interferences may improve the speed and accuracy of the analyses.

6.3.2 Ongoing Studies

Methods to reduce detection limits, decrease interferences by other elements, and investigate applications of different separation methods for arsenic species are being pursued (FEDRIP 1998).

7. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines pertaining to arsenic and its metabolites in air, water, and other media are summarized in Table 7-1.

ATSDR has derived a chronic oral MRL of 0.0003 mg/kg/day for inorganic arsenic based on a NOAEL for dermal effects in humans (Tseng 1977; Tseng et al. 1968) and a provisional acute oral MRL of 0.005 mg/kg/day for inorganic arsenic based on gastrointestinal effects and facial edema in humans (Mizuta et al. 1956).

EPA's Integrated Risk Information System (IRIS) lists an oral reference dose (RfD) of 0.0003 mg/kg/day for arsenic (IRIS 1999). No reference concentration (RfC) for chronic inhalation exposures to arsenic was reported.

The Department of Health and Human Services (DHHS) has determined that inorganic arsenic is a known carcinogen. The EPA has determined that inorganic arsenic is a human carcinogen and has assigned it the cancer classification, Group A (IRIS 1999). EPA's quantitative estimates of carcinogenic risk from oral exposures include a cancer slope factor of 1.5 mg/kg/day and a drinking water unit risk of 0.00005 µg/L. The inhalation unit risk for cancer is 0.0043 µg/m3) (IRIS 1999). The International Agency for Research on Cancer (IARC) cites sufficient evidence of a relationship between exposure to arsenic and human cancer. The IARC classification of arsenic is Group 1 (IARC 1987). The American Conference of Governmental Industrial Hygienists (ACGIH) classifies arsenic (elemental and inorganic compound) as a confirmed human carcinogen; cancer category A1 (ACGIH 1998).

Several arsenic compounds have been designated as "extremely hazardous substances" or "hazardous substances" pursuant to the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) of 1980 (EPA 1995b, 1996c). The owner or operator of any facility that produces, uses, or stores any extremely hazardous substance or CERCLA hazardous substance in an amount exceeding the "threshold planning quantity" is required to immediately report any release to any environmental media, if the amount released is equal to or exceeds the specified "reportable quantity" assigned to the substance. As extremely hazardous substances, when arsenic compounds are formulated as solids, they are subject to either of two threshold planning quantities (EPA 1996c). If the solid exists in powdered form and has a particle size less than 100 microns, it is subject to the lower number. If the solid does not meet this criteria, it is subject to the higher number. Under this rule, the threshold planning quantity for arsenous

pentoxide and arsenous oxide is the same at 10 and 10,000 pounds (4.54 and 4,540 kg) (EPA 1996c). The threshold planning quantity for arsenous trichloride is 500 pounds (270 kg). The reportable quantity for each of these three compounds is 1 pound (0.454 kg) (EPA 1995b). Approximately 11 arsenic compounds are designated as "hazardous substances" under Sections 101(14) and 102(a) of CERCLA and must meet the requirements for reporting releases to the environment in accordance with 40 CFR 302.4. The statutory sources for this designation include Sections 307(a) and 311(b)(4) of the Clean Water Act (CWA), Section 3001 of the Resource Conservation and Recovery Act (RCRA), and Section 112 of the Clean Air Act (CAA) (EPA 1995b). The reportable quantities for these compounds are given in Table 7-1 (EPA 1995b).

The statutory requirements of the CAA also contain a mandate for EPA to evaluate and control emissions of hazardous air pollutants (HAPs). Section 112(b)(1) of the Act includes a list of substances that have been designated as HAPs. The mandate requires EPA to identify specific categories of sources (new and existing) that emit or have the potential to emit these substances to the environment and to promulgate emissions standards for each source. Inorganic arsenic compounds have been identified and listed as HAPs (U.S. Congress 1990). The source categories to which emission standards for arsenic apply include primary copper smelters (EPA 1986g, 1998e), arsenic trioxide and metallic arsenic production facilities (EPA 1986a), glass manufacturing plants (EPA 1990g), primary lead smelters (EPA 1998d), and the Portland cement manufacturing industry (EPA 1998c). Arsenic also appears on the list of toxic chemicals subject to Section 313 of the "Emergency Planning and Community Right-to-Know-Act of 1986" (EPA 1995a).

The discharge of arsenic in the waste waters from point sources is regulated by the Effluent Guidelines and Standards provided in Subchapter N of Title 40 of the Code of Federal Regulations (40 CFR). The statutory authority for these regulations is the CWA. Pursuant to the Act, these regulations prescribe effluent limitations guidelines for existing sources, standards of performance for new sources, and pretreatment standards for new and existing sources (EPA 1981b). The point source categories for which arsenic and arsenic compounds are regulated include inorganic chemical manufacturing (EPA 1982a), nonferrous metals manufacturing (EPA 1990a), timber products processing (EPA 1981b), and electrical and electronic components manufacturing (EPA 1983a). On February 6, 1998, the EPA published a proposed rule which represented the Agency's first effort to develop CWA national effluent limitations guidelines and standards for waste water discharges from commercially-operated hazardous waste combustor facilities that are regulated as "incinerator" or "boilers and industrial furnaces" under RCRA. These facilities would make up a defined subcategory of the waste combustors point source category

(EPA 1998b). Arsenic is also regulated as a waste water pollutant in discharges from new and existing facilities that manufacture metallo-organic active ingredients (EPA 1996a). The limitation for the discharge of pollutants to navigable waters is zero (EPA 1996a).

Under the authority of RCRA, arsenic and arsenic compounds are regulated as the hazardous constituent(s) in several listed hazardous wastes (EPA 1997d). On May 26, 1998, the EPA published in the *Federal Register* a final rule which promulgated "Land Disposal Restrictions" treatment standards for metal-bearing wastes, including wastes found to be hazardous because they exhibit the toxicity characteristic, and hazardous wastes from mineral processing (EPA 1998f). The promulgated standards known as the "universal treatment standards" (UTS) are based on technologies that have been demonstrated to be effective in reducing contaminant levels in metal-bearing wastes or similar wastes (EPA 1998f). For waste waters identified by the hazardous waste code DOO4, the promulgation established a UTS of 1.4 mg/L for arsenic (EPA 1998f).

In order to protect the groundwater within the boundaries of facilities that treat, store, or dispose (TSDFs) of hazardous waste, the EPA has included arsenic on a list of hazardous constituents to be regulated through permissible concentration limits. Owners and operators of TSDFs must not allow the ground-water concentration of a hazardous constituent to exceed the background level for that constituent. The concentration of arsenic in groundwater within the boundaries of a facility must not exceed 0.05 mg/L, as long as the background concentration is below this value (EPA 1997b).

The EPA has a current maximum contaminant level (MCL) of 0.05 mg/L for arsenic in drinking water (EPA 1995e), and has recently proposed reducing the MCL to 0.005 mg/L (EPA 2000b). The World Health Organization (WHO) has established a provisional guideline value of 0.01 mg/L for arsenic in drinking water (WHO 1996).

The Occupational Safety and Health Administration (OSHA) sets permissible exposure limits (PELs) to protect workers against adverse health effects resulting from exposure to hazardous substances. The PELs determined for hazardous substances are enforceable, regulatory limits on allowable indoor air concentrations. OSHA requires employers of workers who are occupationally exposed to these hazardous substances to institute engineering controls and work practices to reduce and maintain employee exposure to at or below the PEL. An employer must ensure that no employee's exposure to inorganic arsenic is greater than 10 $\mu g/m^3$ when averaged over any 8-hour work shift (OSHA 1996b). OSHA also specifies conditions under which employees must be provided with respirators that reduce their exposure to arsenic

and arsenicals (e.g., arsenic trichloride and arsenic phosphide) to below the PEL. The concentrations of inorganic arsenic or conditions of use, and the required respirator type are given in 29 CFR 1910.1018. The requirements applicable to exposures to inorganic arsenic during construction work and for shipyard personnel are identical to those given above (OSHA 1996a, 1996c). However, for exposures to organic arsenic compounds, employers must meet the requirements that OSHA provides for occupational health and environmental controls. These requirements indicate that the exposure of employees to organic arsenic compounds in gases, vapors, fumes, dust, and mist through inhalation, ingestion, skin absorption, or contact should not exceed the "Threshold Limit Values of Airborne Contaminants for 1970" as established by the ACGIH. The ACGIH limits exposure to organic arsenic compounds to 0.5 mg/m^3 as provided in its list of "Threshold Limit Values of Airborne Contaminants for Construction" (OSHA 1997). For biological monitoring of exposures occurring in the workplace, the ACGIH provides a biological exposure index (BEI) of 50 µg/g creatinine. The BEI for a substance applies to 8-hour exposures, for 5 days/week (ACGIH 1998). The National Institute for Occupational Safety and Health (NIOSH) has established a recommended exposure level of 0.002 mg/m^3 (ceiling; 15 minutes) (NIOSH 1997).

Table 7-1. Regulations and Guidelines Applicable to Arsenic

Agency	Description	Information	References
INTERNATIONAL Guidelines:			
IARC	Carcinogenic classification (Arsenic and arsenic compounds)	Group 1[a]	IARC 1987
WHO	Provisional Guideline Value for Drinking Water	0.01 mg/L	WHO 1996
NATIONAL Regulations and Guidelines:			
a. Air			
ACGIH	TLV-TWA Arsenic, elemental and inorganic compounds	0.01 mg/m^3	ACGIH 1999
NIOSH	Recommended exposure limit Arsenic, inorganic compounds	0.002 mg/m^3	NIOSH 1999
OSHA	8-Hour Time weighted average Arsenic, organic compounds	0.5 mg/m^3	29 CFR 1910.1000 OSHA 1999a
	8-Hour Time weighted average permissible exposure limit Arsenic, inorganic compounds	10 $\mu g/m^3$	29 CFR 1910.1018 OSHA 1999b
	8-Hour Time weighted average for construction workers Arsenic, organic compounds	0.5 mg/m^3	29 CFR 1926.55 OSHA 1999d
	8-Hour Time weighted average for shipyard workers Arsenic, organic compounds	0.5 mg/m^3	29 CFR 1915.1000 OSHA 1999c
USC	List of hazardous air pollutants— Arsenic, inorganic compounds, arsine	Yes	42 USC 7412 USC 1999
b. Water			
EPA	Maximum contaminant levels for community waters systems— Arsenic	0.05 mg/L	40 CFR 141.11 EPA 1999b
	Proposed MCL for community water systems—Arsenic	0.005 mg/L	65 FR 38888 EPA 2000b
	Water Quality Criteria Freshwater [b]: Saltwater [b]:	 150 µg/L 36 µg/L	EPA 1999e

Table 7-1. Regulations and Guidelines Applicable to Arsenic *(continued)*

Agency	Description	Information	References
NATIONAL *(contd)*			
b. Water *(contd)*			
EPA *(contd)*			
	Human health consumption of:		EPA 1999e
	water and organism[c]	0.018 µg/L	
	organism only[c]	0.14 µg/L	
FDA	Bottled water limit for arsenic	0.05 mg/L	21 CFR 165.110 FDA 1999a
c. Food			
FDA	Indirect food additive—used in animal feed as animal drugs (percent by weight of feed)		21 CFR 510.515 FDA 1999b
	Arsanilic acid	0.005<x<0.01%	
	Sodium arsanilate	0.005<x<0.01%	
	3-Nitro-4-phenylhydroxy-arsonic acid	0.0025<x<0.005%	
d. Other			
ACGIH	Arsenic, elemental and inorganic		ACGIH 1999
	Cancer classification		
	Biological Exposure Indices	A1[d]	
	Inorganic arsenic metabolites in urine	50 µg/g creatinine	
	Inorganic arsenic plus methylated metabolites in urine[e]	30 µg As/L	
EPA	Arsenic and inorganic compounds		IRIS 1999
	Carcinogenic classification	Group A[f]	
	RfD (oral)	$3x10^{-4}$ mg/kg-day	
	Oral slope factor	1.5 (mg/kg)/day	
	Drinking water unit risk	$5x10^{-5}$ µg/L	
	Inhalation unit risk	$4.3x10^{-3}$ µg/m^3	
	Reportable quantities of hazardous substances		40 CFR 302.4 EPA 1999c
	Arsenic—regarded as a CERCLA hazardous substance under 307(a) and 112 of the Clean Water Act	1 pound	40 CFR 302.4 EPA 1999c
	Arsenic acid—regarded as a CERCLA hazardous substance under section 311(b)(4) of the Clean Water Act	1 pound	40 CFR 302.4 EPA 1999c

Table 7-1. Regulations and Guidelines Applicable to Arsenic *(continued)*

Agency	Description	Information	References
NATIONAL *(contd)* d. Other *(contd)* EPA *(contd)*			
	Sodium arsenite—regarded as a CERCLA hazardous substance under section 311(b)(4) of the Clean Water Act	1 pound	40 CFR 302.4 EPA 1999c
	Arsenic pentoxide—regarded as a CERCLA hazardous substance under section 311(b)(4) of the Clean Water Act; and by RCRA section 3001	1 pound	40 CFR 302.4 EPA 1999c
	Arsenic trioxide—regarded as a CERCLA hazardous substance under section 311(b)(4) of the Clean Water Act	1 pound	40 CFR 302.4 EPA 1999c
	Calcium arsenate—regarded as a CERCLA hazardous substance under section 311(b)(4) of the Clean Water Act; and by RCRA section 3001	1 pound	40 CFR 302.4 EPA 1999c
	Listed as a CERCLA hazardous substance—dimethylarsinic acid	Yes	40 CFR 302.4 EPA 1999c
	Identification and Listing of Hazardous Waste—arsenic, arsenic acid, arsenic pentoxide, arsenic trioxide	Yes	40 CFR 261.33 EPA 1999d
	Toxic Chemical Release Reporting—effective date for arsenic	1/1/87	40 CFR 372.65 EPA 1999a
	Designated hazardous substance in accordance with section 311(b)(2)(a) of the Act—arsenic pentoxide, arsenic trioxide, calcium arsenate, and sodium arsenite	Yes	40 CFR 116.4 EPA 1998h
	Toxic pollutant designated pursuant to section 307(a)(1) of the Act	Yes	40 CFR 401.15 EPA 1998i

Table 7-1. Regulations and Guidelines Applicable to Arsenic *(continued)*

Agency	Description	Information	References
NATIONAL *(contd)* d. Other *(contd)* EPA *(contd)*			
	Statutory Designation as a Hazardous Substance	Yes	Title III Clean Water Act U.S. Congress 1977
	Pesticides severely restricted in the United States	Yes	EPA 1998a
STATE Regulations and Guidelines:			
a. Air			
Arizona	Acceptable concentrations— Arsenic and compounds 1-Hour 24-Hour. Annual Arsenic pentoxide and trioxide 24–Hour Annual	 $3.2x10^{-1}$ µg/m^3 $8.4x10^{-2}$ µg/m^3 $2.3x10^{-4}$ µg/m^3 $5.0x10^{-4}$ µg/m^3 $2.0x10^{-4}$ µg/m^3	NATICH 1992
Connecticut	Acceptable concentrations— 8-hour for arsenic and compounds	 $5.0x10^{-2}$ µg/m^3	NATICH 1992
Florida	Acceptable concentrations— Arsenic and compounds 8-Hour - Fort Lauderdale 8-Hour - Pinella 24-Hour - Pinella Annual - Pinella	 $2.0x10^{-3}$ mg/m^3 2.0 µg/m^3 $4.8x10^{-1}$ µg/m^3 $2.3x10^{-4}$ µg/m^3	NATICH 1992
Idaho	Acceptable ambient concentration for a carcinogen	$2.3x10^{-4}$ µg/m^3	ID Dept Health Welfare 1999b
Kansas	Acceptable concentrations— Arsenic and compounds Annual	 $2.3x10^{-4}$ µg/m^3	NATICH 1992
	Concentration limits for hazardous air emissions	0.005 tons/year	KS Dept. Health Environ 1998b
Louisiana	Acceptable concentrations— Arsenic and compounds Annual	 $2.0x10^{-2}$ µg/m^3	NATICH 1992
Michigan	Acceptable concentrations— Arsenic and compounds Annual	 $2.3x10^{-4}$ µg/m^3	NATICH 1992

Table 7-1. Regulations and Guidelines Applicable to Arsenic *(continued)*

Agency	Description	Information	References
STATE *(contd)*			
a. Air *(contd)*			
Montana	Acceptable concentrations— Arsenic and compounds		NATICH 1992
	Annual	$7.0x10^{-2}$ µg/m^3	
	24-Hour	$3.9x10^{-1}$/µg/m^3	
Nevada	Acceptable concentrations— Arsenic and compounds		NATICH 1992
	Annual	$5.0x10^{-3}$ mg/m^3	
New York	Acceptable concentrations— Arsenic and compounds		NATICH 1992
	Annual	$6.7x10^{-1}$ µg/m^3	
North Carolina	Annual Acceptable concentrations— Arsenic and compounds, arsenic acid and arsenic pentoxide, trichloride, trioxide, trisulfide	$2.3x10^{-7}$ mg/m^3	NATICH 1992
North Dakota	Acceptable concentrations— Arsenic and compounds		NATICH 1992
	8–Hour	$2.0x10^{-3}$ mg/m^3	
Oklahoma	Acceptable concentrations— Arsenic and compounds		NATICH 1992
	24–Hour	$2.0x10^{-2}$ µg/m^3	
Pennsylvania	Acceptable concentrations— Arsenic and compounds		NATICH 1992
	Annual	$2.4x10^{-2}$ µg/m^3	
Rhode Island	Acceptable concentrations— Arsenic and compounds		RI Dept Environ Management 1992
	Annual	0.002 µg/m^3	
South Carolina	24-hour Acceptable concentrations—Arsenic and compounds, and arsenic pentoxide	1.0 µg/m^3	NATICH 1992
Texas	Acceptable concentrations— Arsenic and compounds		NATICH 1992
	30–minute	5.0 µg/m^3	
	Annual	$5.0x10^{-1}$ µg/m^3	
Vermont	Acceptable concentrations— Arsenic and compounds		NATICH 1992
	Annual	$2.3x10^{-4}$ µg/m^3	

Table 7-1. Regulations and Guidelines Applicable to Arsenic *(continued)*

Agency	Description	Information	References
STATE *(contd)*			
a. Air *(contd)*			
Virginia	Acceptable concentrations— Arsenic and compounds 24–Hour Arsenic trisulfide 24-Hour	 3.3 µg/m^3 2.0 µg/m^3	NATICH 1992
Washington	Acceptable concentrations— Arsenic and compounds Annual	 2.3x10^{-4} µg/m^3	NATICH 1992
Wisconsin	Hazardous air contaminants without acceptable ambient concentration requiring lowest achievable emission rate	25 pounds/yr[2]	WI Dept Natural Resources 1997
b. Water			
Alabama	Drinking water quality standards and guidelines	50 µg/L	FSTRAC 1995
	Aquatic life criteria: Freshwater acute Freshwater chronic Marine acute Marine chronic Human health criteria for the consumption of: water and organism[g] organism only[g]	 360 µg/L 190 µg/L 69 µg/L 36 µg/L 1.64x10^{-4} mg/L 3.0x10^{-4} mg/L	AL Dept Environ Management 1998
Alaska	Maximum contaminant level	0.05 mg/L	AK Dept Environ Conserv 1999
Arizona	Water guideline and standard	50 µg/L	FSTRAC 1995
	HBGLs for ingestion of contaminants in drinking water Oral HBGL MCL	 0.02 µg/L 50 µg/L	AR Dept Health Services 1999
Colorado	Aquatic life based criteria for surface waters: Acute Chronic Human health based for drinking water	 360 µg/L 150 µg/L 50 µg/L	CO Dept Public Health Environ 1999

Table 7-1. Regulations and Guidelines Applicable to Arsenic *(continued)*

Agency	Description	Information	References
STATE *(contd)*			
b. Water *(contd)*			
Hawaii	Health guidelines applicable to all water:		HI Dept Health 1999a
	Freshwater		
	acute	360 µg/L	
	chronic	190 µg/L	
	Saltwater		
	acute	69 µg/L	
	chronic	36 µg/L	
	Fish consumption	NS[h]	
	MCL applicable to all public water systems	0.05 mg/L	HI Dept Health 1999b
Idaho	Ground water quality standards	0.05 mg/L	ID Dept Health Welfare 1999a
Illinois	Aquatic based water quality standards:		IL Environ Protec Agency 1999
	acute	360 µg/L	
	chronic	190 µg/L	
Kansas	Surface water quality standards for aquatic life:		KS Dept Health Environ 1998a
	Arsenic		
	acute	Not given	
	chronic	50 mg/L	
	Arsenic(III)		
	acute	379 mg/L	
	chronic	50 mg/L	
	Arsenic(V)		
	acute	850 mg/L	
	chronic	48 mg/L	
Maine	Standard	30 µg/L	FSTRAC 1990
Massachusetts	Standard	50 µg/L	FSTRAC 1990
Minnesota	Guideline	0.2 µg/L	FSTRAC 1995
New Jersey	Groundwater quality arsenic, total	0.02 µg/L	NJ Dept Environ Protec 1993
Oklahoma	Criteria for surface water designated as public and private water supplies	0.10 mg/L	OK Dept Environ Quality 1997
	Aquatic life criteria		OK Dept Environ Quality 1997
	acute	360 µg/L	
	chronic	190 µg/L	
Rhode Island	Standard	50 µg/L	FSTRAC 1990

Table 7-1. Regulations and Guidelines Applicable to Arsenic *(continued)*

Agency	Description	Information	References
STATE *(contd)*			
b. Water *(contd)*			
South Dakota	Maximum contaminant levels—apply to community and non-transient and non-community water systems	0.05 mg/L	SD Dept Environ Natural Resources 1998
Vermont		50 µg/L	FSTRAC 1995
c. Other			
Louisiana	Devil's Swamp and Bayou Baton rouge—wildlife advisory applying to the general population	All fish species	EPA 1997e
Oregon	Willamette river—1,000 feet around the McCormack and Baxter wood treatment site—enforcing a commercial fishing ban	Shellfish-crayfish	EPA 1997e
Washington	Ostrich Bay—wildlife advisory recommending no consumption by the general population	Shellfish-crab, Shellfish, and all bottomfish	EPA 1997e

[a]Group 1=Carcinogenic to humans; classification applies to the group of compounds as a whole but not necessarily to each individual compound in the group.
[b]Freshwater and saltwater criteria for metals are expressed in terms of the dissolved metal in the water column
[c]This criteria applies to inorganic arsenic only, it is currently being reassessed by the Environmental Protection Agency and it is based on carcinogenicity of 10^{-6} risk.
[d]Confirmed human carcinogen
[e]Notice of intended change
[f]Confirmed human carcinogen
[g]The following equations were used to calculate the values as given in the Alabama State laws:

Consumption of water and organism:

Concentration (mg/L) = (HBW x RL)/(CPF x [(FCR x BCF) + WCR])

Consumption of organism only:

Concentration (mg/L) = (HBW x RL)/(CPF x FCR x BCF)

HBW = human body weight, set at 70 kg
RL = risk level, set at $1x10^{-5}$
CPF = cancer potency factor, 1.75 (kg-day)/mg
FCR = fish consumption rate, set at 0.030 kg/day
BCF = bioconcentration factor, 44 L/kg for toluene
WCR = water consumption rate, set at 2 L/day

[h]NS: no standard has been developed as yet.

ACGIH = American Conference of Governmental Industrial Hygienists; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; FSTRAC = Federal State Toxicology and Regulatory Alliance committee; IARC = International Agency for Research on Cancer; MCL = maximum contaminants level; NATIC = National Air Toxics Information Clearinghouse; NIOSH = National Institute of Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; RfD = Oral Reference Dose; TLV = Threshold Limit Value; TWA = time-weighted average; USC = United States Code; WHO = World Health Organization

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9. GLOSSARY

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

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

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

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

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

Benchmark Dose (BMD)—is usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{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—is a statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

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

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

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

Carcinogen—A chemical capable of inducing cancer.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Immunological Effects—are functional changes in the immune response.

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

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

***In Vivo*—**Occurring within the living organism.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 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—is the science of quantitatively predicting the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism and excretion of chemicals by the body.

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

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

Physiologically Based Pharmacokinetic (PBPK) Model—is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates and, possibly membrane permeabilities. The models also utilize biochemical information 4such 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).

Raynaud's Disease--paroxysmal bilateral cyanosis of the digits due to arterial or arteriolar contraction.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from

data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of one can be used; however a reduced UF of three may be used on a case-by-case basis, three being the approximate logarithmic average of 10 and 1.

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

APPENDIX A

ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

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

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

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

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

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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name(s): Inorganic Arsenic
CAS number(s): 7440-38-2
Date: September 2000
Profile status: Camera Ready
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Key to figure: 29
Species: Human
MRL (provisional): 0.005 [X] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: Mizuta N, Mizuta M, Ito F, et al. 1956. An outbreak of acute arsenic poisoning caused by arsenic-contaminated soy-sauce (shÇyu): A clinical report of 220 cases. Bull Yamaguchi Med Sch 4(2-3):131-149.

Experimental design: Mizuta et al. (1956) summarized findings from 220 poisoning cases associated with an episode of arsenic contamination of soy sauce in Japan. The soy sauce was contaminated with approximately 0.1 mg As/mL, probably as calcium arsenate. Arsenic intake in the cases was estimated by the researchers to be 3 mg/day (0.05 mg/kg/day, assuming 55 kg average body weight for this Asian population). Duration of exposure was 2–3 weeks in most cases. Clinical symptoms were recorded. Seventy patients were examined opthalmologically. Laboratory tests were performed on some patients and included hematology, urinalysis, fecal exam, occult blood in gastric and duodenal juice, biochemical examination of blood, liver function tests, electrocardiograph, and liver biopsy.

Effects noted in study and corresponding doses: The primary symptoms were edema of the face, and gastrointestinal and upper respiratory symptoms initially, followed in some patients by skin lesions and neuropathy. Other effects included mild anemia and leukopenia, mild degenerative liver lesions and hepatic dysfunction, abnormal electrocardiogram, and ocular lesions. For derivation of the acute oral MRL, facial edema and gastrointestinal symptoms (nausea, vomiting, diarrhea), which were characteristic of the initial poisoning and then subsided, were considered to be the critical effects.

Dose and end point used for MRL derivation: 0.05 mg As/kg/day

[ ] NOAEL [X] LOAEL

Uncertainty factors used in MRL derivation:

[ ] 1 [ ] 3 [X] 10 (for use of a LOAEL)
[ ] 1 [ ] 3 [ ] 10 (for extrapolation from animals to humans)
[X] 1 [ ] 3 [ ] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain: N/A

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: N/A

Was a conversion used from intermittent to continuous exposure?
If so, explain: N/A

Other additional studies or pertinent information that lend support to this MRL: The MRL is supported by the case of a man and wife in upstate New York who experienced gastrointestinal symptoms (nausea, diarrhea, abdominal cramps) starting almost immediately after beginning intermittent consumption of arsenic-tainted drinking water at an estimated dose of 0.05 mg As/kg/day (Franzblau and Lilis 1989). Gastrointestinal symptoms have been widely reported in other acute arsenic poisoning reports as well, although in some cases, the doses were higher and effects were severe, and in other cases, dose information was not available. The UF of 1 for intrahuman variability reflects the fact that the database includes persons of various ethnicities and age groups, including infants. The MRL is considered provisional because the gastrointestinal effects (nausea, vomiting, diarrhea, and occult blood in feces and gastric and duodenal juice) are serious and because serious neurological (hypesthesia in legs, abnormal patellar reflex) and cardiovascular (abnormal electrocardiogram) effects also occurred at the same dose. Although it is not customary to base an MRL on a serious LOAEL, public health concerns regarding arsenic suggested that a provisional value derived from these data would be useful for the general public.

Agency Contact (Chemical Manager): Selene Chou

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name(s): Inorganic Arsenic
CAS number(s): 7440-38-2
Date: September 2000
Profile status: Camera Ready
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Key to figure: 114
Species: Human
MRL: 0.0003 [X] mg/kg/day [ ] ppm [ ] mg/m^3

References: Tseng, WP, Chu HM, How SW, et al. 1968. Prevalence of skin cancer in an endemic area of chronic arsenicism in Taiwan. J Natl Cancer Inst 40:453–463

Tseng, WP. 1977. Effects and dose-response relationships of cancer and Blackfoot disease with arsenic. Environ Health Perspect 19:109–119.

Experimental design: Tseng et al. (1968) and Tseng (1977) investigated the incidence of Blackfoot disease and dermal lesions (hyperkeratosis and hyperpigmentation) in a large number of poor farmers (both male and female) exposed to high levels of arsenic in well water in Taiwan. A control group consisting of 17,000 people as identified. The authors stated that the incidence of dermal lesions increased with dose, but individual doses were not provided. However, incidence data were provided based on stratification of the exposed population into low (<300 µg/L), medium (300–600 µg/L), or high (>600 µg/L) exposure levels. Doses were calculated from group mean arsenic concentrations in well water, assuming the intake parameters described by Abernathy et al. (1989). Accordingly, the control, low-, medium-, and high-exposure levels correspond to doses of 0.0008, 0.014, 0.038, and 0.065 mg As/kg/day, respectively. The NOAEL identified by Tseng (1977) (0.0008 mg As/kg/day) was limited by the fact that the majority of the population was less than 20 years of age and the incidence of skin lesions increased as a function of age, and because the estimates of water intake and dietary arsenic intake are highly uncertain. Schoof et al. (1998) estimated that dietary intakes of arsenic from rice and yams may have been 15–211 µg/day (mean 61 µg/day), based on arsenic analyses of foods collected in Taiwan in 1993–1995. Use of the 50 µg/day estimate would result in an approximate doubling of the NOAEL (0.016 mg/kg/day).

Effects noted in study and corresponding doses: A clear dose-response relationship was observed for characteristic skin lesions:

0.0008 mg As/kg/day = control group (NOAEL)
0.014 mg As/kg/day = hyperpigmentation and keratosis of the skin (less serious LOAEL)
0.038–0.065 mg As/kg/day = increased incidence of dermal lesions

Dose and end point used for MRL derivation: 0.0008 mg As/kg/day

[X] NOAEL [ ] LOAEL

Uncertainty factors used in MRL derivation:

[ ] 1 [ ] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [ ] 3 [ ] 10 (for extrapolation from animals to humans)

[ ] 1 [x] 3 [ ] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain: The arithmetic mean concentration of arsenic in well water for the control group (0.009 mg/L) was converted to a NOAEL of 0.0008 mg As/kg/day as described below:

$$\left[\left(\frac{0.009\ \text{mg}}{\text{L}} \times \frac{4.5\ \text{L}}{\text{day}}\right) \% \frac{0.002\ \text{mg}}{\text{day}}\right] /55\ \text{kg}\ '\ 0.0008\ \text{mg As/kg/day}]$$

This NOAEL conversion assumed a water intake of 4.5 L/day and a body weight of 55 kg, and includes an estimation of arsenic intake of 0.002 mg As/kg/day from food. These assumptions are detailed in Abernathy et al. (1989). This approach to deriving a chronic oral MRL is identical to EPA's approach to deriving a chronic oral RfD.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: N/A

Was a conversion used from intermittent to continuous exposure?
If so, explain:

Other additional studies or pertinent information that lend support to this MRL: The MRL is supported by a number of well conducted epidemiological studies which identify reliable NOAELs and LOAELs for dermal effects. Chakraborty and Saha (1987) identified a LOAEL of 0.019 mg As/kg/day for melanosis and keratosis for a population in India. Southwick et al. (1981) identified a NOAEL of 0.006–0.007 mg As/kg/day for dermal lesions in several small populations in Utah. Harrington et al. (1978) identified a NOAEL of 0.003 mg As/kg/day for dermal effects in a small population in Alaska. Mazumder et al. (1988) identified a NOAEL of 0.009 mg As/kg/day and a LOAEL of 0.006 mg As/kg/day for pigmentation changes and hyperkeratosis in a small population in India. Cebrian et al. (1983) identified a NOAEL of 0.0004 mg As/kg/day and a LOAEL of 0.022 mg As/kg/day in 2 regions in Mexico. Borgono and Greiber (1972) and Zaldivar (1974)identified a LOAEL of 0.02 mg As/kg/day for abnormal skin pigmentation in patients in Chile, and Borgono et al. (1980) identified a LOAEL of 0.01 mg As/kg/day for the same effect in school children in Chile. Valentine et al. (1985) reported a NOAEL of 0.02 mg As/kg/day for dermal effects in several small populations in California. Collectively, these studies indicate that the threshold dose for hyperpigmentation and hyperkeratosis is approximately 0.01 mg As/kg/day.

Agency Contact (Chemical Manager): Selene Chou

APPENDIX B

USER'S GUIDE

Chapter 1

Public Health Statement

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

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

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

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

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 2-1 and Figure 2-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-1

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

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

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

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

(5) Species The test species, whether animal or human, are identified in this column. Section 2.5, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 2.3, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

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

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

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

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

(10) Reference The complete reference citation is given in chapter 8 of the profile.

(11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious

effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

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

LEGEND

See Figure 2-1

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

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

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

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

(16) NOAEL In this example, 18r NOAEL is the critical endpoint for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

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

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

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

SAMPLE

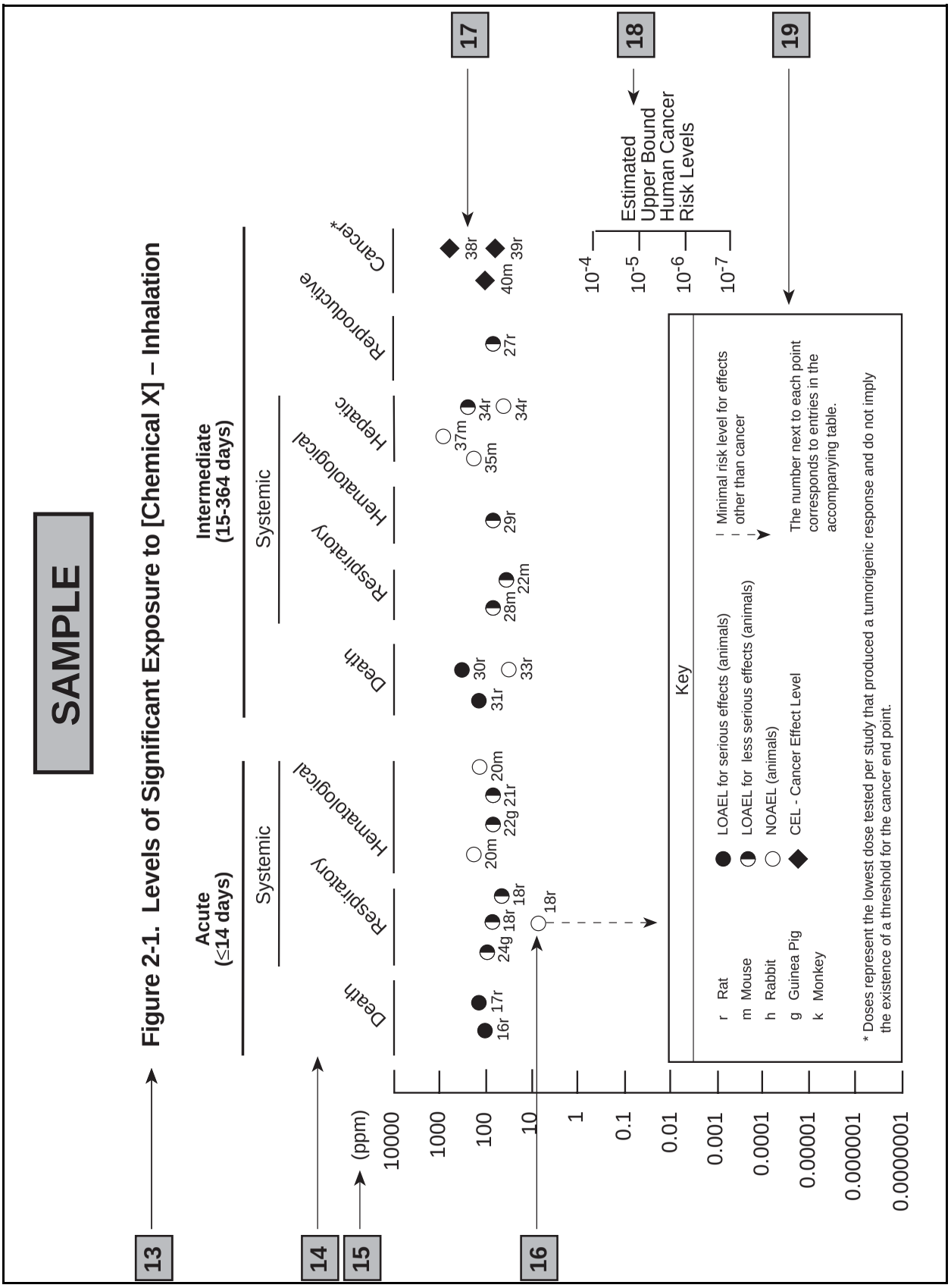
1 6

TABLE 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation

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

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

12 6 [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5 x 10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).


SAMPLE
Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation
Acute (≤14 days)
Intermediate (15-364 days)
Systemic
Respiratory
Hematological
Hepatic
Reproductive
Death
Cancer*
(ppm)
10000
1000
100
10
1
0.1
0.01
0.001
0.0001
0.00001
0.000001
0.0000001
Estimated Upper Bound Human Cancer Risk Levels
10^{-4}
10^{-5}
10^{-6}
10^{-7}
Key
LOAEL for serious effects (animals)
LOAEL for less serious effects (animals)
NOAEL (animals)
CEL - Cancer Effect Level
r Rat
m Mouse
h Rabbit
g Guinea Pig
k Monkey
Minimal risk level for effects other than cancer
The number next to each point corresponds to entries in the accompanying table.
* Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer end point.
13
14
15
16
17
18
19

Relevance to Public Health

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

1. What effects are known to occur in humans?

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

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

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

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

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

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2.5, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.8, "Interactions with Other Substances," and 2.9, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).
To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable

quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADI	Acceptable Daily Intake
ADME	Absorption, Distribution, Metabolism, and Excretion
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	Best Available Technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BSC	Board of Scientific Counselors
C	Centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	Cancer Effect Level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CNS	central nervous system
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
d	day
Derm	dermal
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/International Maritime Dangerous Goods Code
DWEL	Drinking Water Exposure Level
ECD	electron capture detection
ECG/EKG	electrocardiogram

EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
ft	foot
FR	*Federal Register*
g	gram
GC	gas chromatography
Gd	gestational day
gen	generation
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
hr	hour
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LT_{50}	lethal time, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	*trans,trans*-muconic acid
MAL	Maximum Allowable Level
mCi	millicurie
MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
mg	milligram
min	minute
mL	milliliter

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

pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	Pretreatment Standards for New Sources
REL	recommended exposure level/limit
RfC	Reference Concentration
RfD	Reference Dose
RNA	ribonucleic acid
RTECS	Registry of Toxic Effects of Chemical Substances
RQ	Reportable Quantity
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
sec	second
SIC	Standard Industrial Classification
SIM	selected ion monitoring
SMCL	Secondary Maximum Contaminant Level
SMR	standard mortality ratio
SNARL	Suggested No Adverse Response Level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	Total Organic Compound
TPQ	Threshold Planning Quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
VOC	Volatile Organic Compound
yr	year
WHO	World Health Organization
wk	week

>	greater than
≥	greater than or equal to
=	equal to
<	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