DRAFT
TOXICOLOGICAL PROFILE FOR
BORON

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

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UPDATE STATEMENT

A Toxicological Profile for Boron and Boron Compounds was released in 1992. This present edition supersedes any previously released draft or final profile.

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

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

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FOREWORD

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

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

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

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

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

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

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

Comments should be sent to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine
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The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on December 7, 2005 (70 FR 72840). For prior versions of the list of substances, see *Federal Register* notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17, 1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); February 28, 1994 (59 FR 9486); April 29, 1996 (61 FR 18744); November 17, 1997 (62 FR 61332); October 21, 1999 (64 FR 56792); October 25, 2001 (66 FR 54014); and November 7, 2003 (68 FR 63098). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

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

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QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

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

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

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

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

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

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

Other Sections of Interest:

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

ATSDR Information Center

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

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

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

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

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

Other Agencies and Organizations

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

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

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

Referrals

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

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

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

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

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

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

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

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PEER REVIEW

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

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

2. Curtis Eckhert, Ph.D., University of California Los Angeles, Los Angeles, California; and

3. Joseph Landolph, Ph.D., University of Southern California, Los Angeles, California.

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

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

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

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about boron and the effects of exposure to it.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites are then placed on the National Priorities List (NPL) and are targeted for long-term federal clean-up activities. Boron and boron compounds have been found in at least 164 of the 1,689 current or former NPL sites, respectively. Although the total number of NPL sites evaluated for this substance is not known, the possibility exists that the number of sites at which boron is found may increase in the future as more sites are evaluated. This information is important because these sites may be sources of exposure and exposure to this substance may harm you.

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

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

What is boron?

Naturally occurring	Boron is a widely occurring element in minerals found in the earth's crust. It is the 51st most common element found in the earth's crust and is found at an average concentration of 8 mg/kg (approximately 0.0008%).
Combines with oxygen to form borates	Boron is found in the environment primarily combined with oxygen in compounds called borates. Common borate compounds include: • boric acid • sodium tetraborates (also referred to as borax) • boron oxide
Used to manufacture industrial and consumer products	Borate-containing minerals are mined and processed to produce borates for several industrial uses in the United States including: • glass and ceramics • soaps and detergents • fire retardants • pesticides

More information on the properties and uses of boron and boron compounds and how they behave in the environment may be found in Chapters 4, 5, and 6.

What happens to boron when it enters the environment?

Released into air, water, and soil	Boron can be released into air, water, or soil after natural weathering of soils and rocks. Smaller amounts of boron can be released from: • glass manufacturing plants • coal-burning power plants • copper smelters • agricultural fertilizer and pesticide usage.
Is not broken down	Boron cannot be destroyed in the environment. It can only change its form or become attached or separated from particles in soil, sediment, and water.

For more information on boron in the environment, see Chapter 6.

How might I be exposed to boron?

Food	You can be exposed to boron in food, mainly vegetables and fruits. The average daily intake of boron for adults is 1 milligram.
Water	Boron is widely distributed in surface water and groundwater. • the average surface water concentration is about 0.1 mg per liter (mg/L) • boron concentrations in ground water can be as high as 300 mg/L in areas with natural boron-rich deposits • concentrations up to 0.4 mg/L have been found in most drinking water samples.
Soil	Average concentrations of 26 and 33 mg per kilogram (mg/kg) have been reported in soil.
Air	The general public is not likely to be exposed to air contaminated with boron. The average level of boron in air samples is 0.00005 mg boron per cubic meter of air (mg boron/m^3).
Workplace air	In workplaces that mine and process borates, boron concentrations in dusty air samples have been reported to range from about 0.5 to 3 mg boron/m^3.
Consumer products	Boric acid, anhydrous sodium tetraborate, and sodium tetraborate decahydrate (borax) are found in consumer products such as: • laundry detergent • pesticides • facial creams and cleaners • plant foods • household cleaners

Further information on how you might be exposed to boron is given in Chapter 6.

How can boron enter and leave my body?

Most ingested boron is absorbed	Boron can enter your body when you eat food (fruit and vegetables), drink water containing it, when you breathe borate dust in the air, and when damaged skin comes in contact with it.
Typically leaves your body within 4 days	Most of the boron leaves the body in urine. Over half of the boron taken by mouth can be found in urine within 24 hours and the other half can be detected in urine for up to 4 days.

Further information on how boron enters and leaves the body is given in Chapter 3.

How can boron affect my health?

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

The effect of boron on human health depends on how much boron is present, how you are exposed to it, and the length of exposure.

Exposure in air	People working in dusty workplaces where borates are mined and processed have reported irritation of the nose, throat, and eyes. The irritation does not persist for long periods after leaving the dusty area.
Exposure by ingestion	*Humans*: Exposure to large amounts of boron (about 30 g of boric acid) over short periods of time can affect the stomach, intestines, liver, kidney, and brain and can eventually lead to death. *Animals:* Studies of dogs, rats, and mice indicate that the male reproductive organs, especially the testes, are affected if large amounts of boron are ingested for short or long periods of time. The doses that produced these effects in animals are more than 1,800 times higher than the average daily intake of born in food by adults in the U.S. population. No evidence of cancer was found in a study in which mice were given boric acid in the diet throughout their lifetime.

More information on the health effects of boron in humans and animals can be found in Chapters 2 and 3.

How can boron affect children?

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

Children are likely to have similar effects as adults	It is likely that children would show the same health effects as adults. We do not know whether children differ in their susceptibility to the effects of boron.
Birth defects	We do not know whether boron causes birth defects in people. Low birth weights, birth defects, and developmental delays have occurred in newborn animals whose mothers were orally exposed to high doses of boron (as boric acid). The doses that produced these effects in pregnant animals are more than 800 times higher than the average daily intake of boron in food by adult women in the U.S. population

How can families reduce the risk of exposure to boron?

Boron is part of the natural environment and you will have some exposure from foods and drinking water.

Limit children's exposure to pesticides	Pesticides containing boron compounds should be used according to their directions and should be kept away from children.
Store household chemicals out of reach of young children	Always store household chemicals in their original labeled containers out of reach of young children to prevent accidental poisonings. Never store household chemicals in containers children would find attractive to eat or drink from, such as old soda bottles.
Discourage children from eating dirt or putting hands in their mouth while playing with dirt	Children living near waste sites containing boron and boron compounds are likely to be exposed to higher than normal environmental levels of boron through breathing in boron-containing dust, touching soil, and eating contaminated soil. Children should be encouraged to wash their hands frequently, especially before eating.

Is there a medical test to determine whether I have been exposed to boron?

Can be measured in blood and urine	Blood and urine can be examined to determine whether excessive exposure to boron has occurred. The detection of boron in the blood or urine cannot be used to predict the kind of health effects that might develop from that exposure.

Further information on how boron can be measured in exposed humans is presented in Chapters 3 and 7.

What recommendations has the federal government made to protect human health?

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

Regulations and recommendations can be expressed as "not-to-exceed" levels, that is, levels of a toxic substance in air, water, soil, or food that do not exceed a critical value that is usually based on levels that

affect animals; they are then adjusted to levels that will help protect humans. Sometimes these not-to-exceed levels differ among federal organizations because they used different exposure times (an 8-hour workday or a 24-hour day), different animal studies, or other factors.

Recommendations and regulations are also updated periodically as more information becomes available. For the most current information, check with the federal agency or organization that provides it.

Some regulations and recommendations for boron include the following:

Levels in drinking water set by EPA	The EPA has determined that exposure to boron in drinking water at concentrations of 4 mg/L for one day or 0.9 mg/L for 10 days is not expected to cause any adverse effects in a child. The EPA has determined that lifetime exposure to 1 mg/L boron is not expected to cause any adverse effects.
Levels in workplace air set by OSHA	OSHA set a legal limit of 15 mg/m^3 for boron oxide in air averaged over an 8-hour work day.

Additional information on governmental regulations regarding boron can be found in Chapter 8.

Where can I get more information?

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

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

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

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

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

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

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2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO BORON IN THE UNITED STATES

Boron is a widely occurring element in minerals found in the earth's crust. It is the 51st most common element found in the earth's crust and is found at an average concentration of 8 mg/kg (approximately 0.0008%). It is found in the environment primarily combined with oxygen in compounds called borates. Common borate compounds include boric acid, salts of boric acid (e.g., sodium tetraborates, which are also referred to as borax), and boron oxide. U.S. borate mining and production mainly occurs in Kern, San Bernardino, and Inyo Counties, California. Borate-containing minerals are mined and processed to produce borates for several industrial uses in the United States. Industrial uses include glass and ceramics (70%), soaps and detergents (4%), fire retardants (2%), and agriculture (2%). Other uses, including metallurgy, nuclear applications, sale to distributors, and ingredients in cosmetics or medical preparations, make up the remaining 19%. There are 189 pesticide products registered in the United States that contain boric acid or one of its sodium salts as an active ingredient.

Human exposure to boron, typically as borates or boric acid, may occur through ingestion of food and water, or through use of pesticides containing boron compounds, inhalation of boron-containing powders or dusts, or the use of boron from cosmetics or medical preparations. The most appreciable boron exposure to the general population is likely to be through ingestion of food and, to a lesser extent, water. Mean daily intakes of boron for male and female adults were reported to be 1.17 and 0.96 mg boron/day. Consumption of fruits and vegetables contribute largely to boron intake in the human diet. Boron levels reported in drinking water generally range from >1 to 3 mg boron/liter.

Boron concentrations in ambient air samples have been reported to range from $<5x10^{-7}$ to $8x10^{-5}$ mg boron/m^3, with an average concentration of $2x10^{-5}$ mg boron/m^3. Workers in other industries, including manufacture of fiberglass and other glass products, cleaning and laundry products, fertilizers, pesticides, and cosmetics, may also be exposed to boron compounds. Mean dust concentrations ranging from 3.3 to 18 mg particulates/m^3 were measured in air samples from U.S. facilities where borax was packaged and shipped. Dust samples in these facilities were predominantly composed of various types of borates and ranged from 11.8 to 15.2% boron by weight. Using the midpoint of this range of boron percentages in the dusts (13.5% boron), boron concentrations in air from these workplaces are estimated to have ranged from 0.45 to 2.43 mg boron/m^3. In another study of dust concentrations in air samples from a U.S. borax production facility, mean total dust concentrations ranged from 0.29 to 18.95 mg particulates/m^3

(approximately 0.02 to 1.50 mg boron/m^3, using the midpoint (7.9%) of the ranges of average boron content in these dusts).

The average surface water boron concentration in the United States is about 0.1 mg boron/L, but concentrations vary greatly, depending on boron content of local geologic formations and anthropogenic sources of boron. Several studies have measured boron concentrations in water in those areas of California with boron-rich deposits. Reported high boron concentrations in surface waters ranged from 15 mg boron/L in coastal drainage waters to 360 mg boron/L in a boron-rich lake. Groundwater boron concentrations >100 mg boron/L are common in California. Average concentrations of 26 and 33 mg boron/kg soil have been reported in soils in the United States, with concentrations ranging up to 300 mg boron/kg. For a more complete discussion of possible exposures to boron, see Chapter 6 of the profile.

2.2 SUMMARY OF HEALTH EFFECTS

The primary health effects associated with inhalation exposure of humans to boron are acute respiratory and ocular irritation. Acute-duration exposures of mining and processing workers to 0.44–3.1 mg boron/m^3 (5.7–14.6 mg particulates/m^3) as sodium borate dusts has been associated with mild irritation of the eyes, throat, and nose, as well as cough and breathlessness. No exposure-related changes in lung function were observed in nonsmoking workers; a decrease in 1 second forced expiratory volume (FEV_1) was observed in workers who smoked and were exposed to higher concentrations of boron. However, a re-examination of the workers 7 years later did not result in boron-related alterations in lung function. Similar symptoms and signs of upper respiratory tract irritation have been observed in exercising volunteers exposed for short durations (<1 hour) to 1.5 mg boron/m^3 as sodium borate dusts.

Animal studies of inhalation exposure to boron are restricted to a series of studies that found no histological changes in a comprehensive examination of tissues (including the respiratory tract) from rats exposed to aerosols of boron oxide (6 hours/day, 5 days/week) at concentrations of 73 mg boron/m^3 for 10 weeks, 27 mg boron/m^3 for 12 weeks, or 12 mg boron/m^3 for 24 weeks. There was some indication of local irritation of the external nares in rats exposed to 73 mg boron/m^3 for 10 weeks. A limited examination of dogs exposed to 9 mg boron/m^3 did not find hematological alterations or evidence of liver damage, evaluated using the sulfobromophthalein retention test.

In contrast, diborane gas (B_2H_4) is a potent respiratory tract toxicant. Exposure of mice to diborane gas at a concentration of 5 ppm diborane (1.7 mg boron/m^3) for 2 weeks produced severe damage to the lungs

including pulmonary congestion, bleeding, and edema. Slight changes (infiltration of polymorphous neutrophil in peribronchiolar region) were observed at 0.7 ppm diborane (0.2 mg boron/m^3). However, diborane gas is expected to have a very short half-life in the environment and is not expected to be a significant environmental toxicant, except in workplaces where it might be used or manufactured and accidentally released.

Human case reports have shown that boron can be lethal following short-term oral exposure at high doses, although the variability in human responses to acute exposure is quite large. The minimal lethal dose of ingested boron (as boric acid) was reported to be 2–3 g in infants, 5–6 g in children, and 15–20 g in adults. However, a review of 784 human poisonings with boric acid (10–88 g) reported no fatalities, with 88% of cases being asymptomatic. Liver, kidney, central nervous system, and gastrointestinal effects and skin lesions have been found in lethal cases following ingestion of boron, but death has been attributed to respiratory failure. Surveys of Turkish and Chinese populations with elevated levels of borate salts in drinking water (9–25 mg boron/liter) found no associations for chronic-duration exposure with reproductive effects. The essentiality of boron has been established for most plants and some animals, but not in humans. The use of boron as a dietary supplement has not been endorsed by the Food and Nutrition Board/Institute of Medicine and did not result in increased plasma testosterone or strength levels in bodybuilders.

Oral exposure animal studies have clearly identified the reproductive system and developing fetus as the most sensitive targets of boron toxicity. Adverse developmental effects have been identified for acute- and intermediate-duration exposures. Decreases in the number of live fetuses and litters, decreases in body weight, and increases in the occurrence of external, visceral, and cardiovascular malformations were observed in the fetuses of rabbits administered 44 mg boron/kg/day on gestation days 6–19; no developmental effects were observed at 22 mg boron/kg/day. Following intermediate-duration exposure, decreases in body weight and increases in the occurrence of skeletal malformations have been observed in the fetuses of rats exposed to 13 mg boron/kg/day on gestation days 0–20; a NOAEL of 10 mg boron/kg/day was identified. Reproductive effects have been observed at higher doses. Histological alterations in the testes and sperm effects have been observed in rats administered 88 mg boron/kg/day for 2 weeks; the NOAEL was 44–53 mg boron/kg/day. Intermediate-duration exposure resulted in histological alterations in the testes and associated effects on spermatogenesis in rats exposed to doses of ≥26 mg boron/kg/day. No viable sperm were observed in male rats exposed to 101 mg boron/kg/day for 14 weeks. Impaired ovulation and failure to conceive was also observed in female rats (mated with unexposed males) exposed to 116 mg boron/kg/day for 14 weeks prior to mating. A no-observed-

adverse-effect level (NOAEL) of 30 mg boron/kg/day was identified for what reproductive effects in males in a 3-generation rat study. Testicular atrophy has also been observed in rats exposed to 81 mg boron/kg/day and mice exposed to 201 mg boron/kg/day for 2 years; no testicular alterations were observed at 24 or 79 mg boron/kg/day, respectively.

In addition to the developmental and reproductive effects, several systemic effects have been observed in orally exposed animals. Consistently observed effects following intermediate and chronic exposure include hematological alterations (decreases in hemoglobin levels and splenic hematopoeisis) and desquamated skin on the paw; these effects have been observed at doses of ≥60 mg boron/kg/day. Chronic inflammation and coagulative necrosis have also been observed in the livers of mice exposed to 79 mg boron/kg/day for 2 years.

The primary health effects associated with dermal exposure are irritation of the eyes and reversible skin changes. Case reports of human occupational exposures have suggested that acute dermal exposure to boron as borax may cause focal alopecia of the scalp. However, as this effect has been reported in only three cases with no estimate of dose and involved co-exposure to high levels of other organic solvents, this association is uncertain. In animals, ocular instillation of 50 mg boron oxide (7.8 mg boron) dust resulted in conjunctivitis, while instillation of a sodium perborate monohydrate solution containing 6.3 mg boron into the eyes of rabbits caused mild irritancy of the epithelium and superficial stroma.

No epidemiology studies have identified an association between boron exposure and development of cancer. However, some investigators have suggested that boron exposure in drinking water may be associated with lower incidences of some types of cancer in humans. Intermediate-duration oral exposure of boric acid to mice that had been implanted with prostate tumor cells resulted in significantly reduced tumor growth and reduced tumor serum antigen levels. Chronic-duration oral studies in rats, mice, and dogs involving dietary exposure to boric acid or borax have not found significant increases in neoplastic lesions. *In vitro* genotoxicity assays have given predominantly negative results. The International Agency for Research on Cancer (IARC), the National Toxicology Program (NTP), and EPA have not classified boron for human carcinogenicity.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for boron. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an

appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

Inhalation MRLs

- An MRL of 0.01 mg/m^3 has been derived for acute-duration inhalation exposure (14 days or less) to boron.

The available information on the toxicity of inhaled boron comes from an occupational exposure study (Wegman et al. 1994) and a human experimental study (Cain et al. 2004). Both studies identified respiratory irritation as a sensitive target of toxicity. Nose, eye, and throat irritation was observed in workers at a borax processing facility exposed to a 6-hour time-weighted average (TWA) concentration of 0.44 mg boron/m^3 (Wegman et al. 1994) and nasal and throat irritation was observed in volunteers exposed to 1.5 mg boron/m^3 for 20 minutes while exercising (Cain et al. 2004); neither study identified a NOAEL for respiratory effects. The identification of the respiratory tract as the most sensitive target of toxicity is supported by longer-term animal studies (Wilding et al. 1959) that found no adverse systemic effects in rats or dogs exposed to higher concentrations (9–72 mg boron/m^3).

The Wegman et al. (1994) study was selected as the basis of the acute-duration inhalation MRL for boron because it identified a lower LOAEL than the Cain et al. (2004) study and involved a longer-duration exposure. This study (Wegman et al. 1994) of 106 workers at a borax processing facility examined the correlation of workplace incidences of symptoms of acute eye and respiratory irritation (nose, throat, cough, breathlessness) with measurements of average sodium borate dust levels. The study population

was comprised of 79 exposed and 27 comparison workers. Constant personal air sampling was performed to monitor sodium borate (anhydrous, pentahydrate, decahydrate) levels in each worker's environment. Reported symptoms were given severity scores of 0 (not at all) to 10 (maximal). Results were adjusted for age, smoking, and the presence of common cold. A mean daily total boron exposure of 0.44 mg/m^3 (5.72 mg/m^3 total borate dust exposure) in the exposed group, compared with 0.02 mg/m^3 (0.45 mg/m^3 total borate dust exposure) in the comparison group, resulted in 2–9-fold increases ($p>0.001$) in incidences of eye and respiratory irritation (nasal irritation > breathlessness > eye irritation > throat irritation > cough). In the exposed group, 96% of incidences were given a severity score of ≤4. Given the relatively low severity of reported symptoms in the exposed group, the observed respiratory irritation is considered a minimally adverse effect. The mean severity score in the unexposed group was 1.9. This study was well-conducted and clearly associated irritation effects with quantitative estimates of borate dust exposure.

An acute-duration inhalation MRL of 0.01 mg boron/m^3 was derived using the lowest-observed-adverse-effect level (LOAEL) of 0.44 mg boron/m^3 for eye, nasal, and throat irritation, cough, and breathlessness in workers. The LOAEL of 0.44 mg/m^3 was divided by an uncertainty factor of 30 (3 for use of a minimally adverse LOAEL and 10 for human variability).

A series of studies conducted by Wilding et al. (1959) examined the toxicity of boron following intermediate-duration exposure of rats. No adverse effects, as assessed by a histological examination of a comprehensive set of tissues, were observed in rats exposed to aerosols of boron oxide (6 hours/day, 5 days/week) at concentrations of 73 mg boron/m^3 for 10 weeks, 27 mg boron/m^3 for 12 weeks, or 12 mg boron/m^3 for 24 weeks. A reddish exudate from the nose was observed in some of the rats exposed to 73 mg boron/m^3 for 10 weeks; the investigators noted that the rats were covered with dust and there probably was local irritation of the external nares and scratching. Another study by this group (Wilding et al. 1959) found no hematological alterations or alterations in sulfobromophthalein retention for liver damage in dogs exposed to 9 mg boron/m^3 for 23 weeks. Because the NOAELs identified in the rat and dog studies were higher than concentrations associated with irritation in humans acutely exposed to boron (Cain et al. 2004; Wegman et al. 1994), the intermediate-duration inhalation database was considered inadequate for derivation of an MRL. However, these data do suggest that the acute-duration inhalation MRL of 0.01 mg boron/m^3 should be health-protective for intermediate-duration exposures.

There are limited data on the chronic toxicity of boron in humans and no chronic-duration inhalation animal studies. Workers exposed to mean boron concentrations of 1.8 and 3.1 mg boron/m^3 reported a

higher frequency of respiratory symptoms such as dryness of the mouth, nose, or throat, dry cough, nose bleeds, and sore throat than in workers exposed to low levels of boron (0.9 and 0.2 mg boron/m^3) (Garabrant et al. 1984, 1985); this is the same study population examined by Wegman et al. (1994) (see acute MRL discussion). No alterations in lung function, as measured by FEV_1, were observed in nonsmoking workers; a reduced FEV_1 was found in a subgroup of smoking workers with estimated boron exposure of ≥9 mg boron/m^3. In the Wegman et al. (1994) follow-up study, no alterations in lung function were observed 7 years after the initial examination of workers receiving exposures of ≥15 mg boron/m^3. The cross-sectional design of the Garabrant et al. (1985) study prevents determining whether the elevation of respiratory symptoms was a consequence of acute or repeated exposure to sodium borate dusts. Tarasenko et al. (1972) reported revealed low sperm counts, reduced sperm motility, and elevated fructose content of seminal fluids in workers exposed to 22–80 mg/m^3 boron aerosols (boron form uncertain) for ≥10 years; however, interpretation of these results is limited by the small number of subjects and limited data reporting. Another study reported elevated fertility rates, as compared to U.S. national average, in workers employed at a borax production facility for at least 9 months (Whorton et al. 1994); no exposure data were reported. The uncertainty as to whether the effects observed in the Garabrant et al. (1984) study were due to acute or chronic exposure and the limitations in the Tarasenko et al. (1972) study preclude deriving a chronic-duration inhalation MRL for boron. However, the lack of chronic effects in workers observed by Wegman et al. (1994) 7 years after an assessment by Garabrant et al. (1985) suggests that the acute-duration inhalation MRL of 0.01 mg/m^3 should be health-protective for chronic-duration exposures.

Oral MRLs

- An MRL of 0.2 mg/kg/day has been derived for acute-duration oral exposure (1–14 days) to boron.

Acute-duration oral exposures of humans to high levels of boron (as boric acid) have resulted in little or no observable toxicity, as was seen in accidental poisonings of 10–88 g, of which 88% of cases were asymptomatic (Litovitz et al. 1988). However, gastrointestinal, cardiovascular, hepatic, renal, and central nervous system effects, dermatitis, erythema, and death have been observed in children and adults exposed to ≥84 mg boron/kg (Ishii et al. 1993; Restuccio et al. 1992; Schillinger et al. 1982; Wong et al. 1964).

Most of the available animal studies on the acute toxicity of boron have focused on developmental and reproductive toxicity end points. NTP (1987; Dieter 1994) reported gastric hyperplasia and dysplasia in

mice exposed to 2,251 mg boron/kg/day as boric acid in the diet for 14 days; no gastrointestinal effects were observed at 926 mg boron/kg/day. Similarly, Weir and Fisher (1972) reported vomiting in dogs receiving a single gavage dose of 1,000 mg boron/kg/day as boric acid. Testicular and spermatogenic effects were observed in rats receiving gavage doses of 88 mg boron/kg/day for 2 weeks (Fukuda et al. 2000; Kudo et al. 2000). No effects were observed at 44 or 53 mg boron/kg/day.

A series of studies conducted by Cherrington and Chernoff (2002) demonstrate the fetal toxicity of boron in mice. A variety of skeletal malformations (e.g., rib agenesis, fused rib, cervical rib, reduced rib length) were observed in the fetuses of mice receiving gavage doses of 88 mg boron/kg/day on gestation days 6–10, 131 mg boron/kg on gestation day 8, or 70 mg boron/kg administered twice daily on gestation day 8 or 6–8. Two gavage doses of 131 mg boron/kg on gestation day 8 resulted in multiple thoracic skeletal malformations. Reductions in fetal body weights were also observed in these studies and in studies of mice receiving two gavage doses of 70 mg boron/kg on gestation days 6, 7, 9, or 10. However, skeletal malformations were not observed in studies that did not include exposure on gestation day 8. No NOAELs for developmental effects were observed in the Cherrington and Chernoff (2002) studies. A study of rabbits (Price et al. 1996b) identified a lower LOAEL for developmental toxicity. At gavage doses of 44 mg boron/kg/day as boric acid administered on gestation days 6–19, significant increases in resorptions and decreases in the number of live litters and fetuses were observed. This dose was also associated with decreases in fetal body weight and increases (on percent fetuses per litter basis) in external, visceral, and cardiovascular malformations. Marked decreases in maternal body weight were also observed at 44 mg boron/kg/day. No adverse maternal or fetal effects were observed at 22 mg boron/kg/day.

The Price et al. (1996b) study was selected as the principal study for derivation of an acute-duration oral MRL because it identified a lower LOAEL than the Cherrington and Chernoff (2002) studies and involved a longer duration of exposure (14 days compared to 5 days). In the Price et al. (1996b) study, groups of 30 pregnant New Zealand white rabbits were given gavage doses of 0, 62.5, 125, or 250 mg boric acid/kg/day (0, 11, 22, or 44 mg boron/kg/day) on gestation days 6–19. Observations were made for clinical signs, maternal and fetal body weight, number of implantations, resorptions, number of live and dead fetuses, and fetal external, visceral, and skeletal defects. No adverse maternal effects were observed in rabbits in the 11 or 22 mg boron/kg/day groups. At 44 mg boron/kg/day, decreases in maternal body weight, relative kidney weight, and food consumption were observed. During the treatment period, the rabbits lost 137 g body weight compared to a weight gain of 93 g in controls. No differences in the number of implantation sites per litter were observed; however, there were significant

increases in the percent resorptions per litter, percent of litters with one or more resorptions, and percent of litters with 100% resorption. The number of live litters was 18, 23, 20, and 6 in the 0, 11, 22, and 44 mg boron/kg/day groups, respectively, and the number of live fetuses was 159, 175, 153, and 14, respectively. A decrease in fetal body weights (92% of controls) was observed at 44 mg boron/kg/day; although the body weight was not significantly different from controls, the effect was considered biologically significant. Significant increases in the percent of fetuses per litter with external, visceral, and cardiovascular malformations and cardiovascular variations were observed. Although the overall incidence of external malformations was increased at 44 mg boron/kg/day, there were no increases in a specific malformation. The visceral malformations primarily consisted of cardiovascular malformations, particularly interventricular septal defect, enlarged aorta, papillary muscle malformation, and double outlet right ventricle. The cardiovascular variations consisted of abnormal number of cardiac papillary muscles.

An acute-duration oral MRL of 0.2 mg boron/kg/day was derived using the NOAEL of 22 mg boron/kg/day associated with a LOAEL of 44 mg boron/kg/day for increased incidence of external, visceral, and cardiovascular malformations and reduced body weight in the fetuses of rabbits administered boric acid via gavage on gestation days 6–19. The NOAEL of 22 mg boron/kg/day was divided by an uncertainty factor of 100 (10 for interspecies extrapolation and 10 for human variability).

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

There are limited data on the intermediate-duration toxicity of boron in humans. Seizure disorders were observed in infants orally exposed to approximately 12–120 g of borax for 4–12 weeks (Gordon et al. 1973; O'Sullivan and Taylor 1983). The possible association between boron exposure and impaired fertility was investigated in Turkish subpopulations expected to have intermediate- to chronic-duration exposures to boron (Sayli 1998a, 1998b, 2003; Sayli et al. 1998) and boron mining and processing workers, which may have included oral exposure to boron (Chang et al. 2006; Whorton et al. 1994). These studies did not find significant associations.

Animal studies have clearly identified reproductive and developmental toxicity as the most sensitive effects of oral boron exposure. Intermediate-duration exposure of rats, mice, and dogs to boric acid or borax results in histological damage to the testes and the associated impacts on spermatogenesis (sperm abnormalities and reduced sperm production) at doses ≥26 mg boron/kg/day as boric acid (Dieter 1994; Dixon et al. 1976, 1979; Fail et al. 1991; Fukuda et al. 2000; Harris et al. 1992; Ku et al. 1993a; Kudo et

al. 2000; Lee et al. 1978; NTP 1987; Nusier and Bataineh 2005; Seal and Weeth 1980; Weir and Fisher 1972; Yoshizaki et al. 1999). Complete sterility was observed in rats exposed to 101 mg boron/kg/day as boric acid or borax for 14 weeks prior to mating (Weir and Fisher 1972); a lack of viable sperm was observed at this dose level. Additionally, female rats exposed to similar doses (116 mg boron/kg/day) for 14 weeks failed to become pregnant when mated with non-exposed males (Weir and Fisher 1972); the female sterility response at this dose level was associated with decreased ovulation. The Weir and Fisher (1972) 3-generation studies (males and females exposed to boric acid or borax) established a NOAEL of 30 mg boron/kg/day for reproductive toxicity in rats.

The developing fetus appears to be a more sensitive target than the reproductive system. Reductions in fetal body weights were observed in rats following exposure to 13–13.6 mg boron/kg/day as boric acid on gestation days 0–20 (Heindel et al. 1992; Price et al. 1996a); an increase in the occurrence of skeletal abnormalities was also observed at this dose level (Price et al. 1996a). At 28.4 mg boron/kg/day, rib cage defects, enlargement of the lateral ventricles of the brain, and increased resorptions were observed in rats exposed to boric acid on gestation days 0–20 (Heindel et al. 1992). No developmental effects were observed in rats exposed to 10 mg boron/kg/day as boric acid on gestation days 0–20 (Price et al. 1996a). In mice, gestational exposure on days 0–17 resulted in reduced fetal weights at 79 mg boron/kg/day and increased skeletal defects and increased resorptions at 175.3 mg boron/kg/day (Heindel et al. 1992); a NOAEL of 43.4 mg boron/kg/day was identified.

Systemic effects are observed at somewhat higher doses. Hematological alterations (splenic extramedullary hematopiesis and decreased hemoglobin levels) were observed at 60.5 and 72 mg boron/kg/day in dogs and rats, respectively, exposed to as borax or boric acid (NTP 1987; Weir and Fisher 1972), desquamation of paw and tail skin and eye inflammation were observed in rats exposed to 150 mg boron/kg/day as boric acid or borax (Weir and Fisher 1972), and hyperkeratosis and/or acanthosis was observed in rats at 577 mg boron/kg/day as boric acid (NTP 1987).

The available intermediate-duration oral database clearly identifies the developing fetus as the most sensitive target of toxicity. Two studies in rats (Heindel et al. 1992; Price et al. 1996a) identified LOAELs of 13–13.6 mg boron/kg/day for decreases in fetal body weight and skeletal malformations (only identified in the Price et al. 1996a study). These LOAELs are lower than the NOAEL of 30 mg boron/kg/day identified for reproductive toxicity in a 3-generation study (Weir and Fisher 1972) and NOAELs of 35 or 45 mg boron/kg/day for hematological and dermal effects (Weir and Fisher 1972).

Multiple developmental end point data from the Price et al. (1996a) and Heindel et al. (1992) studies were pooled and subjected to multiple benchmark dose analyses (Allen et al. 1996); see Appendix A for summaries of these two studies and the benchmark dose analysis. The 95% lower confidence limit on the benchmark dose associated with a 5% reduction in fetal body weight ($BMDL_{05}$) was calculated to be 10.3 mg boron/kg/day. This estimate was similar to the observed NOAEL of 10 mg boron/kg/day (Price et al. 1996a) and was used as a point of departure for derivation of the intermediate-duration oral MRL. The $BMDL_{05}$ of 10.3 mg boron/kg/day was divided by a chemical-specific uncertainty factor of 66 (3.3 for toxicokinetic extrapolation from animals to humans, 3.16 for toxicodynamic extrapolation from animals to humans, 2.0 for variability in human toxicokinetics, and 3.16 for variability in human toxicodynamics) (see Appendix A for derivation of the chemical-specific uncertainty factor) resulting in an intermediate-duration oral MRL of 0.2 mg boron/kg/day.

2.3.1 Chronic-Duration Oral Studies

As previously discussed, no significant associations between boron exposure and impaired fertility were observed in Turkish subpopulations expected to have intermediate- to chronic-duration exposures to boron (Sayli 1998a, 1998b; Sayli et al. 1998, 2003). Chronic-duration studies have been conducted in rats and dogs exposed to boric acid or borax in the diet (Weir and Fisher 1972) and mice exposed to boric acid in the diet (Dieter 1994; NTP 1987). Systemic effects consisted of hematological alterations (decreases in hemoglobin in rats and splenic hematopoeisis in mice), desquamation of footpad skin and bloody ocular discharge in rats, decreased body weight gain in rats and mice, lung hemorrhage in mice, and hepatic chronic inflammation and coagulative necrosis in mice. The hematological, dermal, ocular, and body weight effects were observed in rats exposed to 81 mg boron/kg/day (NOAEL of 24 mg boron/kg/day). In mice, the hematological and liver effects were observed at 79 mg boron/kg/day and the body weight and lung effects were observed at 201 mg boron/kg/day. The highest dose tested in the dog studies (6.8 mg boron/kg/day) was a NOAEL for systemic effects. Testicular atrophy was observed in rats exposed to 81 mg boron/kg/day as boric acid or borax (Weir and Fisher 1972) and mice exposed to 201 mg boron/kg/day as boric acid (Dieter 1994; NTP 1987); the NOAELs for these effects were 24 and 79 mg boron/kg/day for the rats and mice, respectively. A chronic-duration oral MRL, based on results from the chronic oral toxicity studies in animals, was not derived. However, the intermediate MRL, which is based on developmental toxicity, should be protective for chronic exposure because the NOAEL (24 mg boron/kg/day) for testicular atrophy and systemic effects in chronically exposed rats (Weir and Fisher 1972) was higher than the intermediate-duration LOAELs of 13–13.6 mg boron/kg/day for developmental toxicity in rats (Heindel et al. 1992; Price et al. 1996a).

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3. HEALTH EFFECTS

3.1 INTRODUCTION

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

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

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not

the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

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

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

3.2.1 Inhalation Exposure

Most of the inhalation toxicity data for boron involves human or animal exposure to borate dusts such as boric acid, boron oxide, or various hydration states of sodium borate salts (anhydrous; pentahydrate; and decahydrate; also referred to borax) or other borate salts (e.g., calcium borate). In aqueous media, boron oxide is rapidly transformed to boric acid and, depending on the pH of the media, to borate salts. In addition, animal studies were located reporting the effects of inhaled diborane, a flammable boron-containing gas. Because of the differences in environmental prevalence, industrial uses, likelihood of exposure, and respiratory toxicity, the effects of diborane exposure are discussed separately from other boron compounds in Section 3.2.1.2, Respiratory Effects.

3.2.1.1 Death

No studies were located regarding death in humans after inhalation exposure to boron. The 4-hour LC_{50} for boric acid, borax, and disodium borates is >2 mg boron/m^3 (Hubbard 1998). No fatalities were observed in rats exposed for 6 hours/day, 5 days/week, to 470 mg boron oxide/m^3 (73 mg boron/m^3) for 10 weeks, 175 mg boron oxide/m^3 (27 mg boron/m^3) for 12 weeks, or 77 mg boron oxide/m^3 (12 mg boron/m^3) for 24 weeks, or dogs exposed to 57 mg boron oxide/m^3 (9 mg boron/m^3) for 23 weeks (Wilding et al. 1959).

3.2.1.2 Systemic Effects

No studies were located regarding cardiovascular, gastrointestinal, hematological, musculoskeletal, or renal effects in humans after inhalation exposure to boron. No studies were located regarding dermal effects after acute inhalation exposure in humans or animals for any duration category, but eye irritation has been reported in sodium-borate mining and processing workers. Information on respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, and renal effects in animals and respiratory effects and dermal/ocular effects in humans is discussed below. The highest NOAEL values and all reliable LOAEL values for these systemic effects for each species and duration category involving exposure to boric acid, borates, or boron oxide are recorded in Table 3-1 and plotted in Figure 3-1. Results from a few mouse inhalation studies of diborane gas indicate that it is a potent respiratory toxicant, much more potent than borates or boron oxide. Since it is not expected to be as important an environmental compound as borates or boron oxide, NOAEL and LOAEL values from these mouse studies of diborane gas are not included in Table 3-1 or Figure 3-1.

Respiratory Effects. Occupational studies of workers exposed to dusts of sodium borates, the most important commercial forms of boron, have identified irritation of the respiratory tract and eyes, without measurable changes in pulmonary function. In an early cross-sectional surveillance of 629 U.S. workers in a sodium borate open-pit mining and production plant, past occurrence of symptoms of respiratory irritation such as dryness of the mouth, nose, or throat, dry cough, nose bleeds, and sore throat were reported at elevated frequencies in workers in areas with mean dust concentrations of 8.4 and 14.6 mg particulates/m^3 (1.8 and 3.1 mg boron/m^3, respectively), compared with workers in areas with lower mean dust levels of 4.0 and 1.1 mg particulate/m^3 (0.9 and 0.2 mg boron/m^3) (Garabrant et al. 1984; 1985). In addition, a reduction in forced expiratory volume in 1 second (FEV_1) was measured in a subgroup of smoking workers with estimated high cumulative exposure (≥80 mg particulate/m^3, ≥9 mg boron/m^3) to sodium borate dusts, but not in groups of less-exposed smoking workers or in nonsmoking workers. However, a subsequent surveillance of FEV_1 in 303 of the original 629 borax workers, 7 years after the original surveillance, , some of whom were exposed to ≥15 mg boron/m^3, found no exposure-related changes in FEV_1 over this period, when adjustments were made for the effects of age, height, and smoking on FEV_1 (Wegman et al. 1994). Although the prevalence of workers reporting acute respiratory irritation symptoms increased with the mean dust concentrations for different job categories in the plant, the cross-sectional design of the Garabrant et al. (1985) study prevented the determination of whether the elevation of acute respiratory symptoms was a consequence of acute or repeated exposure to sodium

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Systemic								
1	Human	once 20 min	Resp	0.7 M	1.5 M (mild irritation of nose and throat; increased nasal secretion)		Cain et al. 2004 SODIUM BORATE	
2	Human	6 hr/d TWA (Occup)	Resp		0.44[b] (nasal and throat irritation; cough and breathlessness)		Wegman et al. 1994 SODIUM BORATE	Symptoms were reported on an hourly basis and associated with hourly personal air samples.
			Ocular		0.44 (eye irritation symptoms)			
INTERMEDIATE EXPOSURE								
Systemic								
3	Rat	10 wk 5 d/wk 6 hr/d	Resp		73 (reddish nasal exudate)		Wilding et al. 1959 BORIC OXIDE	Negative histopathology on all examined tissues.
			Cardio	73				
			Gastro	73				
			Hemato	73				
			Musc/skel	73				
			Hepatic	73				
			Renal	73				
			Endocr	73				
			Ocular	73				
			Bd Wt	73				

Table 3-1 Levels of Significant Exposure to Boron - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m^3)	LOAEL Less Serious (mg/m^3)	LOAEL Serious (mg/m^3)	Reference Chemical Form	Comments
4	Rat	12 wk 5 d/wk 6 hr/d	Resp	27			Wilding et al. 1959 BORIC OXIDE	NOAELs are for histopathology or hematology.
			Cardio	27				
			Gastro	27				
			Hemato	27				
			Musc/skel	27				
			Hepatic	27				
			Renal	27				
			Endocr	27				
			Ocular	27				
			Bd Wt	27				

Table 3-1 Levels of Significant Exposure to Boron - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
5	Rat	24 wk 5 d/wk 6 hr/d	Resp	12			Wilding et al. 1959 BORIC OXIDE	NOAELs are for histopathology or hematology.
			Cardio	12				
			Gastro	12				
			Hemato	12				
			Musc/skel	12				
			Hepatic	12				
			Renal	12				
			Endocr	12				
			Ocular	12				
			Bd Wt	12				
6	Dog (NS)	23 wk	Hemato	9			Wilding et al. 1959 BORIC OXIDE	Hematology and serum chemistry values comparable to controls; no histological exams reported.
			Hepatic	9				
Immuno/ Lymphoret								
7	Rat (albino)	12 wk 5 d/wk 6 hr/d		27			Wilding et al. 1959 BORIC OXIDE	NOAEL is for lymph node and spleen histopathology.

Table 3-1 Levels of Significant Exposure to Boron - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
8	Rat (albino)	24 wk 5 d/wk 6 hr/d		12			Wilding et al. 1959 BORIC OXIDE	NOAEL is for lymph node and spleen histopathology.
9	Rat (albino)	10 wk 5 d/wk 6 hr/d		73			Wilding et al. 1959 BORIC OXIDE	Negative lymph node and spleen histopathology.
Neurological								
10	Rat (albino)	10 wk 5 d/wk 6 hr/d		73			Wilding et al. 1959 BORIC OXIDE	NOAEL is for brain histopathology.
11	Rat (albino)	12 wk 5 d/wk 6 hr/d		27			Wilding et al. 1959 BORIC OXIDE	NOAEL is for brain histopathology.
12	Rat	24 wk 5 d/wk 6 hr/d		12			Wilding et al. 1959 BORIC OXIDE	NOAEL is for brain histopathology.
Reproductive								
13	Rat	12 wk 5 d/wk 6 hr/d		27			Wilding et al. 1959 BORIC OXIDE	NOAEL is for testes or ovary histopathology.
14	Rat (albino)	24 wk 5 d/wk 6 hr/d		12			Wilding et al. 1959 BORIC OXIDE	NOAEL is for testes or ovary histopathology.

Table 3-1 Levels of Significant Exposure to Boron - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m^3)	LOAEL			Reference Chemical Form	Comments
					Less Serious (mg/m^3)		Serious (mg/m^3)		
15	Rat	10 wk 5 d/wk 6 hr/d		73				Wilding et al. 1959 BORIC OXIDE	NOAEL is for testes or ovary histopathology.
CHRONIC EXPOSURE									
Systemic									
16	Human	11.4 yr (mean)	Resp		1.8	(dryness of the mouth, nose, or throat, dry cough, nose bleeds, and sore throat)		Garabrant et al. 1984, 1985 SODIUM BORATE	Uncertain whether symptoms were from acute or chronic exposures.

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

b Used to derive an acute-duration inhalation MRL of 0.01 mg boron/m3; exposure level divided by an uncertainty factor of 30 (3 for use of a minimal LOAEL and 10 for human variability).

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = Female; Gastro = gastrointestinal; Hemato = hematological; hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; occup = occupational; Resp = respiratory; TWA = time-weighted average; x = time(s); wk = week(s); yr = year(s)

Figure 3-1 Levels of Significant Exposure to Boron - Inhalation

Acute (≤14 days)

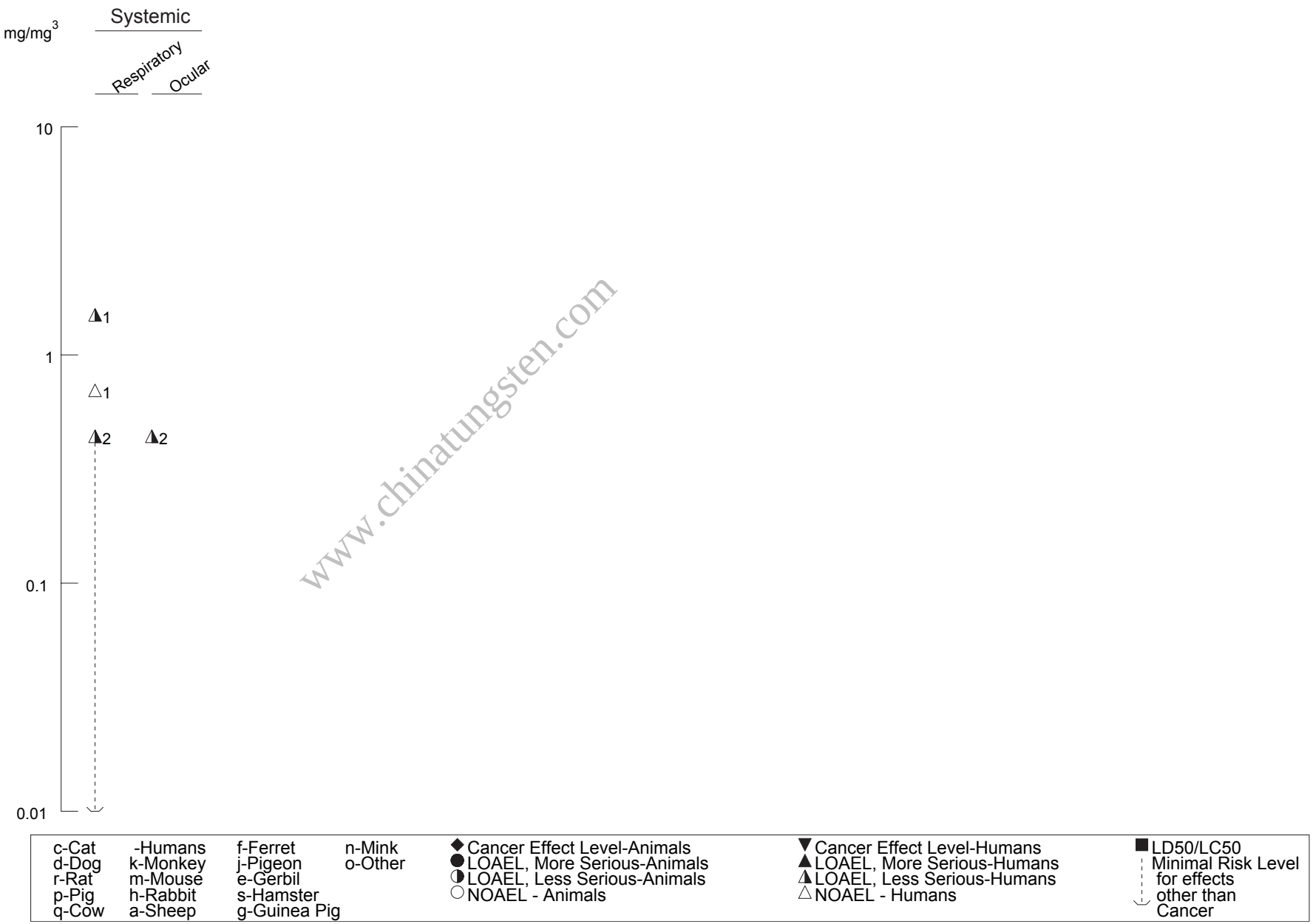


Figure 3-1 Levels of Significant Exposure to Boron - Inhalation *(Continued)*

Intermediate (15-364 days)

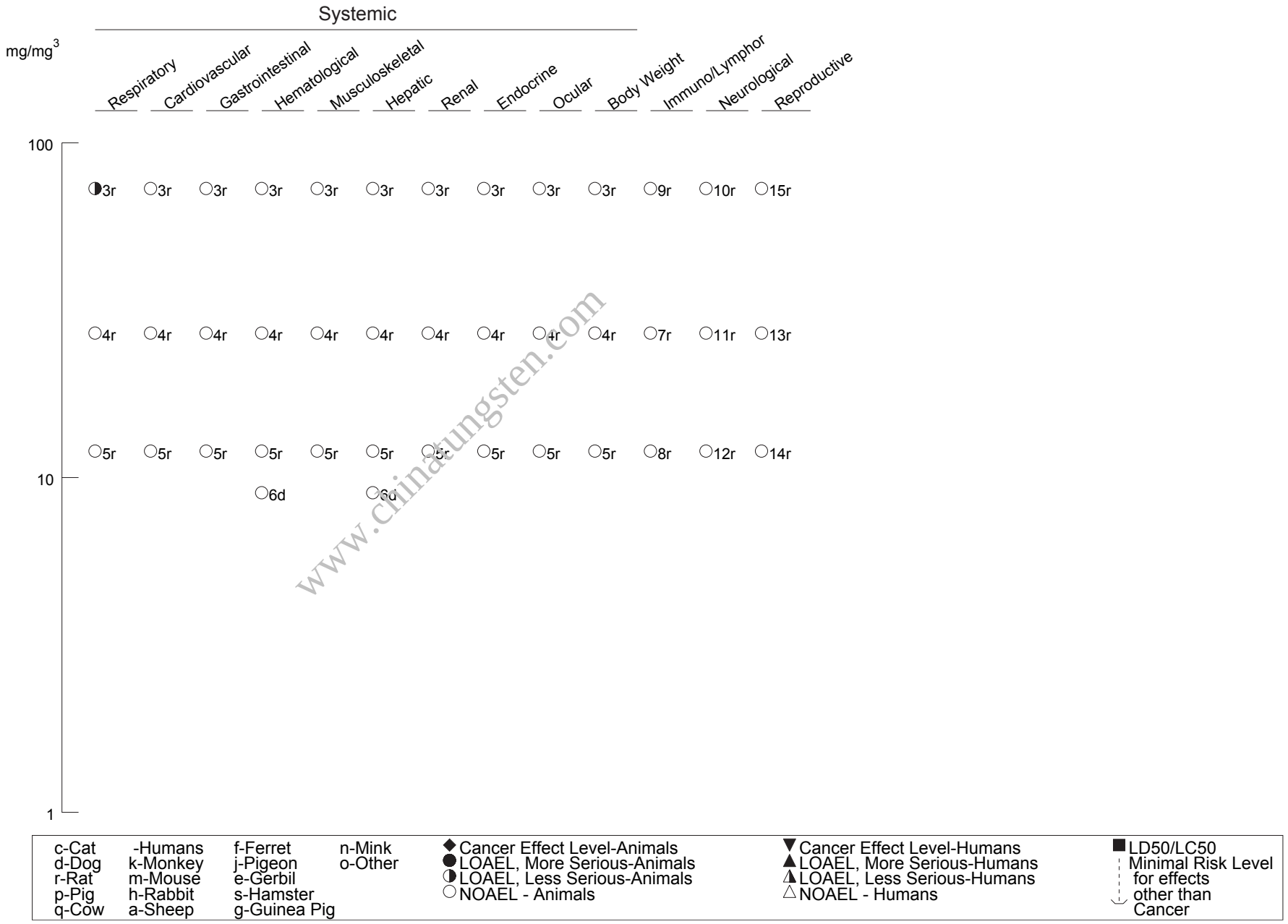
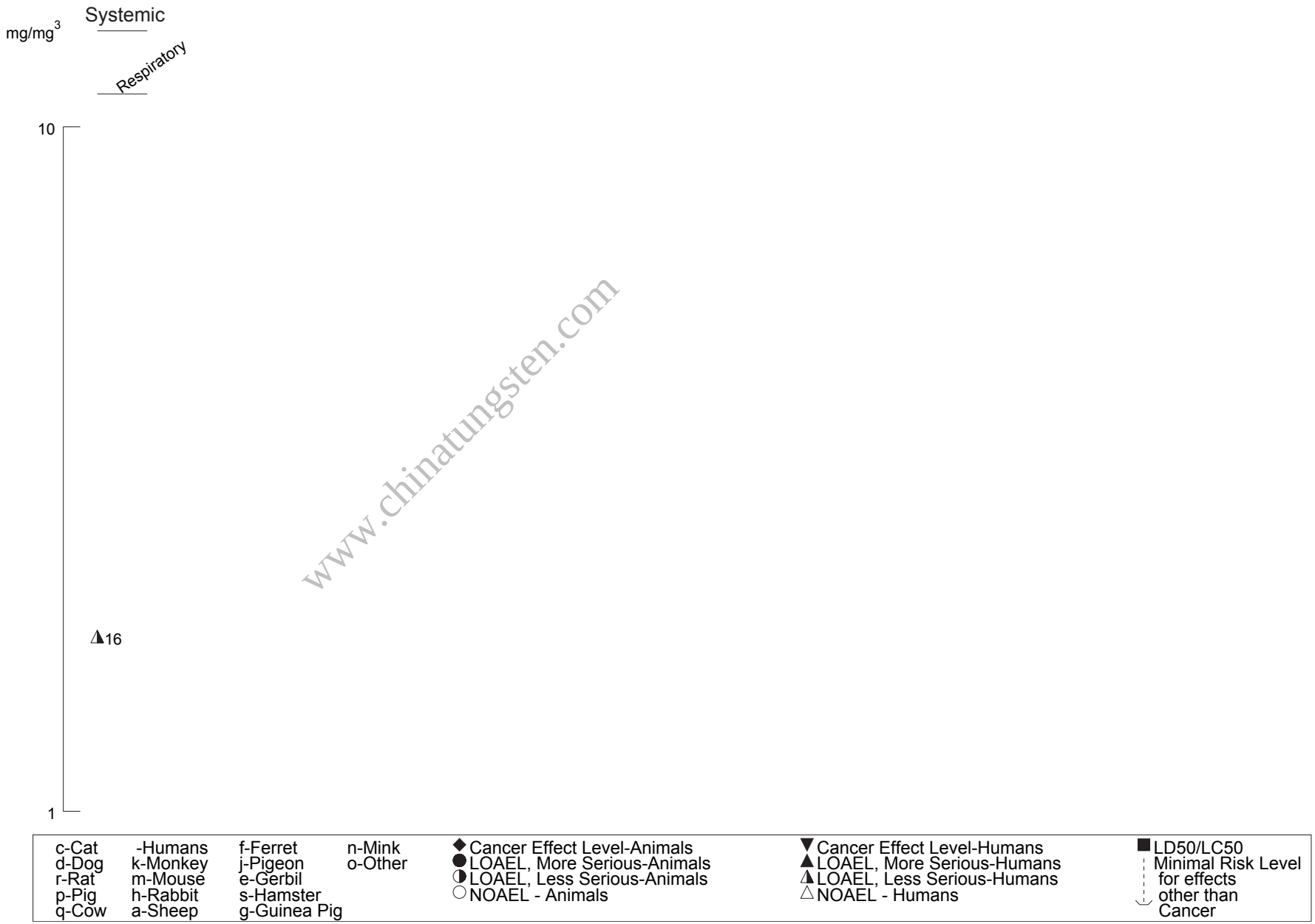


Figure 3-1 Levels of Significant Exposure to Boron - Inhalation *(Continued)*

Chronic (≥365 days)



borate dusts. Thus, the effect levels associated with the measured prevalence of acute respiratory symptoms in this study are not included in Table 3-1 or Figure 3-1.

The occurrence of acute respiratory symptoms as a possible consequence of acute exposure to dusts of sodium borate was studied in a later study by interviewing workers about acute irritation symptoms before the work shift began and at regular hourly intervals during the work shift, and by measuring personal air concentrations of particulates at concurrent intervals for 4 consecutive days (Hu et al. 1992; Wegman et al. 1994). Seventy-nine exposed production workers and 27 nonexposed workers were included in the study. In the latest analysis of the collected data, the incidence rates for irritation symptoms in exposed workers were statistically significantly higher than those in nonexposed workers, with exposed workers 9-, 5-, and 3-fold more likely to report incidents of nasal, eye, and throat irritation, respectively, than comparison workers (Hu et al. 1992; Wegman et al. 1994). The arithmetic means of the time-weighted average (TWA) 6-hour daily dust concentrations were 5.72 mg particulates/m^3 (0.44 mg boron/m^3) for the exposed group and 0.45 mg particulates/m^3 (0.02 mg boron/m^3) for the nonexposed group (Wegman et al. 1994). In the exposed group, 91% of reported symptoms were rated with severity scores ≤3 ("moderate") and 96% of symptoms were rated with severity scores of ≤4 ("pretty much"). In the unexposed group, the average severity score for all symptoms was 1.9 ("very little" to "fairly little"). Thus, the acute respiratory irritation effects are deemed to be minimally adverse. An acute-duration MRL of 0.01mg boron/m^3 was based on irritation of the nose, eye, and throat in workers exposed to a mean 6-hour TWA of 0.44 mg boron/m^3 (5.72 mg particulates/m^3) (Wegman et al. 1994). This study identified the lowest LOAEL for the most sensitive acute-duration effect based on individually-measured boron inhalation exposure levels associated with specific reported irritation responses. Further, since no chronic effects (i.e., reduced FEV_1) were observed in workers assessed by Wegman et al. (1994), 7 years after being assessed by Garabrant et al. (1985), the acute-duration inhalation MRL of 0.01 mg/m^3 should also be health-protective for intermediate- and chronic-duration exposures.

Acute-duration laboratory exposures of volunteers to sodium borate dust support the findings of respiratory irritation reported in the occupational studies. Volunteers exposed to 1.5 mg boron/m^3 (10 mg sodium borate/m^3) for 20 minutes while exercising had significantly increased nasal secretions (by mass) and reported significantly higher perception of nasal and throat irritation compared to controls (Cain et al. 2004). These effects did not occur with exposure to an aerosol concentration of 0.7 mg boron/m^3.

Corroborating evidence in animals for the respiratory irritation potential of inhaled boron compounds is sparse. The only inhalation exposure animal study with a boron compound is one in which rats were exposed to aerosols of boron oxide (6 hours/day, 5 days/week) at concentrations of 470 mg boron oxide/m^3 (73 mg boron/m^3) for 10 weeks, 175 mg boron oxide/m^3 (27 mg boron/m^3) for 12 weeks, or 77 mg boron oxide/m^3 (12 mg boron/m^3) for 24 weeks, and dogs were exposed to 57 mg boron oxide/m^3 (9 mg boron/m^3) for 23 weeks (Wilding et al. 1959). In rats, histological examination of a comprehensive set of tissues revealed no differences between the tissues of exposed and control animals. Signs of gross toxicity were restricted to the appearance of a reddish exudate from the nose of some of the rats exposed to 470 mg boron oxide/m^3.

Mice (ICR) exposed to 0.7 ppm diborane gas (0.2 mg boron/m^3) for 2 or 4 weeks exhibited slight infiltration of polymorphous neutrophil in peribronchiolar regions of the respiratory tract (Nomiyama et al. 1995). Mice exposed to 5 ppm diborane gas (1.7 mg boron/m^3) for 2 weeks exhibited increased lung weight, nasal cavity changes, diffuse panbronchiolitis-like lesions, cellular infiltration of the bronchioles and perivascular area, appearance of alveolar macrophages, perivascular lymphoid hyperplasia, lung congestion, bleeding, and edema (Uemura et al. 1995).

Comparison of the results from the studies of mice exposed to diborane gas (Nomiyama et al. 1995; Uemura et al. 1995) and those from studies of rats and dogs exposed to boron oxide (Wilding et al. 1959) indicate that diborane gas is much more potent as a respiratory toxicant than boron oxide. Diborane gas is expected to have a very short half-life in the environment because of its reactivity. Thus, it is not expected to be a significant environmental toxicant, except in workplaces where it might be used and accidentally released.

Cardiovascular Effects. Rats exposed to aerosols of boron oxide at a concentration of 470 mg boron oxide/m^3 (73 mg boron/m^3) for 10 weeks, 175 mg boron oxide/m^3 (27 mg boron/m^3) for 12 weeks, or 77 mg boron oxide/m^3 (12 mg boron/m^3) for 24 weeks showed no gross or microscopic effects in the cardiovascular system (Wilding et al. 1959).

Gastrointestinal Effects. No gross or microscopic changes were seen in the gastrointestinal tract of rats exposed to aerosols of boron oxide at a concentration of 470 mg boron oxide/m^3 (73 mg boron/m^3) for 10 weeks, 175 mg boron oxide/m^3 (27 mg boron/m^3) for 12 weeks, or 77 mg boron oxide/m^3 (12 mg boron/m^3) for 24 weeks (Wilding et al. 1959).

Hematological Effects. Rats exposed to aerosols of boron oxide at concentrations of 470 mg boron oxide/m^3 (73 mg boron/m^3) for 10 weeks, 175 mg boron oxide/m^3 (27 mg boron/m^3) for 12 weeks, or 77 mg boron oxide/m^3 (12 mg boron/m^3) for 24 weeks, and dogs exposed to aerosols of boron oxide at concentrations of 57 mg boron oxide/m^3 (9 mg boron/m^3) for 23 weeks showed no significant changes in total red and white blood cell count, hemoglobin, hematocrit, or differential count (Wilding et al. 1959).

Musculoskeletal Effects. No gross or microscopic effects of exposure were observed in the femur, rib, and muscle of rats exposed to concentrations of 470 mg boron oxide/m^3 (73 mg boron/m^3) for 10 weeks, 175 mg boron oxide/m^3 (27 mg boron/m^3) for 12 weeks, or 77 mg boron oxide/m^3 (12 mg boron/m^3) for 24 weeks (Wilding et al. 1959).

Hepatic Effects. No gross or microscopic hepatic effects were observed in rats exposed to aerosols of boron oxide at concentrations of 470 mg boron oxide/m^3 (73 mg boron/m^3) for 10 weeks, 175 mg boron oxide/m^3 (27 mg boron/m^3) for 12 weeks, or 77 mg boron oxide/m^3 (12 mg boron/m^3) for 24 weeks. No hepatic effects were indicated from serum chemistry of dogs exposed to aerosols of boron oxide at concentrations of 57 mg boron oxide/m^3 (9 mg boron/m^3) for 23 weeks (Wilding et al. 1959).

Renal Effects. No gross or microscopic renal effects were observed in rats exposed to aerosols of boron oxide at concentrations of 470 mg boron oxide/m^3 (73 mg boron/m^3) for 10 weeks, 175 mg boron oxide/m^3 (27 mg boron/m^3) for 12 weeks, or 77 mg boron oxide/m^3 (12 mg boron/m^3) for 24 weeks. No renal effects were indicated from serum chemistry of dogs exposed to aerosols of boron oxide at concentrations of 57 mg boron oxide/m^3 (9 mg boron/m^3) for 23 weeks (Wilding et al. 1959).

Ocular Effects. Human occupational exposure to a mean concentration of 0.44 mg boron/m^3 (5.72 mg particulates/m^3) (Hu et al. 1992; Wegman et al. 1994) and 1.8–3.1 mg boron/m^3 (8.4–14.6 mg particulates/m^3) (Garabrant et al. 1984, 1985) as sodium borate dust produced eye irritation following acute-duration exposures. The cross-sectional study design of Garabrant et al. (1984, 1985) made it difficult to determine whether the observed effects were caused by acute or repeated exposures; however, the design employed by Wegman et al. (1994), which included 6-hour TWA air samples and worker reports of irritancy before the start of the work shift and during the shift, allowed the determination that this acute ocular irritation was due to acute exposure. No ocular effects were observed in rats exposed to aerosols of boron oxide at concentrations of 470 mg boron oxide/m^3 (73 mg boron/m^3) for 10 weeks, 175 mg boron oxide/m^3 (27 mg boron/m^3) for 12 weeks, or 77 mg boron oxide/m^3 (12 mg boron/m^3) for 24 weeks (Wilding et al. 1959).

3.2.1.3 Immunological and Lymphoreticular Effects

No gross or microscopic effects on immunological or lymphoreticular tissues (lymph nodes and spleens) were observed in rats exposed to aerosols of boron oxide at concentrations of 470 mg boron oxide/m^3 (73 mg boron/m^3) for 10 weeks, 175 mg boron oxide/m^3 (27 mg boron/m^3) for 12 weeks, or 77 mg boron oxide/m^3 (12 mg boron/m^3) for 24 weeks (Wilding et al. 1959).

3.2.1.4 Neurological Effects

No gross or microscopic effects on the brain were observed in rats exposed to aerosols of boron oxide at concentrations of 470 mg boron oxide/m^3 (73 mg boron/m^3) for 10 weeks, 175 mg boron oxide/m^3 (27 mg boron/m^3) for 12 weeks, or 77 mg boron oxide/m^3 (12 mg boron/m^3) for 24 weeks (Wilding et al. 1959).

3.2.1.5 Reproductive Effects

A study of 28 male boric acid production workers occupationally exposed to 22–80 mg/m^3 boron aerosols (boron form uncertain) for ≥10 years (Tarasenko et al. 1972) revealed low sperm counts, reduced sperm motility, and elevated fructose content of seminal fluids, compared to controls. These effects are consistent with high-dose animal exposures. However, this study is limited by the small number of subjects and limited data reporting. Furthermore, a cross-sectional survey of 753 employees working for at least 9 months at a borax production facility in California found worker fertility rates to be higher than the U.S. national average (Whorton et al. 1994). However, this study is limited by lack of exposure data.

In animals, no gross or microscopic effects were found on the ovary or testes of rats exposed to aerosols of boron oxide at concentrations of 470 mg boron oxide/m^3 (73 mg boron/m^3) for 10 weeks, 175 mg boron oxide/m^3 (27 mg boron/m^3) for 12 weeks, or 77 mg boron oxide/m^3 (12 mg boron/m^3) for 24 weeks (Wilding et al. 1959).

3.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals after inhalation exposure to boron.

3.2.1.7 Cancer

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

3.2.2 Oral Exposure

Data for boron oral toxicity in humans involves exposure to the borates or boric acid. These boron-containing compounds are primarily found in food and water and have been implicated in numerous accidental or intentional poisonings in human case reports. Similarly, the boron toxicity studies in animals have utilized exposures to borates or boric acid.

3.2.2.1 Death

Case reports of lethal oral exposure of humans to boron primarily involve accidental or intentional exposures to high levels of boric acid. Similar clinical signs have been seen in adults and children. A review of 784 primarily acute boric acid exposures in adults and children found that 88% of cases were asymptomatic. The reports did not contain information on the dose response for boric acid, as symptomatic cases had doses ranging from 100 mg to 55 g boric acid (18 mg–10 g boron), while asymptomatic cases had doses ranging from 10 mg to 89 g boric acid (2 mg–16 g boron) (Litovitz et al. 1988). Nonetheless, death occurred in some children following oral doses in this wide dose range. Five infants who ingested formula accidentally prepared with 2.5% aqueous solution of boric acid became lethargic, developed vomiting and diarrhea, and died within 3 days after exposure (Wong et al. 1964). The estimated boric acid consumption ranged from 4.51 to 14 g (0.8–2.5g boron). In two infants who ingested 9.25 g boric acid (505 mg boron/kg/day) and 14 g boric acid (765 mg boron/kg/day), degenerative changes were seen in the liver, kidney, and brain (Wong et al. 1964). In a food poisoning incident in Malaysia, 13 children died after consuming Chinese noodles contaminated with boric acid (Chao et al. 1991a, 1991b). The deaths were determined by the study authors to be caused by unknown levels of aflatoxin and boric acid in the noodles. Clinical signs included vomiting, pyrexia, diarrhea, abdominal pain, anorexia, giddiness, seizures, and eventual coma. Postmortem examination revealed coagulative necrosis of the liver, proliferative metaplasia of the hepatocytes, giant cell formation, central vein sclerosis, bile stasis, and steatosis, acute renal tubule necrosis, upper gastrointestinal erosion, and encephalopathy. However, the relative contribution of boric acid to these effects could not be determined.

A common suite of symptoms was presented in case reports of adult oral exposures that resulted in death. A 77-year-old man ingested a single dose of 30 g of boric acid (85 mg boron/kg) to cure hiccups (Ishii et

al. 1993). Effects included vomiting, diarrhea, erythema, cyanotic extremities, acute renal failure, cardiopulmonary hypotension, and death from cardiac insufficiency. Almost identical clinical signs and death occurred in a 45-year-old man ingesting approximately 49 g of boron (280 g boric acid, 700 mg boron/kg assuming a body weight of 70 kg) (Restuccio et al. 1992).

In animals, rats appear to be more sensitive than dogs or mice to the lethal effects of acute boron exposures. Oral LD_{50} values for respective boron equivalents of boric acid or borax were 898 and 642 mg/kg in an unspecified rat strain (Smyth et al. 1969), 600 and 510 mg/kg in Sprague-Dawley rats (Weir and Fisher 1972), and 550 and 690 mg/kg in Long Evans rats (Weir and Fisher 1972). No deaths were reported in dogs exposed to a single dose of 696 mg boron/kg (3,977 mg boric acid/kg) and 738 mg boron/kg (5,549 mg borax/kg) (Weir and Fisher 1972). No single-dose LD_{50} studies in mice were available; however, mortality rates of 20 and 60% were observed in males given 14 daily doses of 2,251 and 3,671 mg boron/kg/day (12.9 or 21.0 g boric acid/kg/day) in the diet, respectively (NTP 1987), but not at 926 mg boron/kg/day (5.3 g boric acid/kg/day). These animals were lethargic and exhibited discolored spleen, liver, and renal medullae and hyperplasia and dysplasia of the forestomach (NTP 1987).

With intermediate-duration oral exposure, rats appear to be slightly more sensitive than mice to the lethality of boric acid. There was 100% mortality in Sprague-Dawley rats fed 450 mg boron/kg/day within a 6-week period (Weir and Fisher 1972). Congestion of liver and kidneys, small gonads, and brain swelling were reported. Eighty percent of male and 60% of female B6C3F1 mice died in a study involving exposure to 577 mg boron/kg/day (3298 mg boric acid/kg/day) in the diet for up to 90 days (NTP 1987). Hyperkeratosis and/or acanthosis in the stomach and extramedullary hematopoiesis of the spleen in both sexes of mice were observed at the same dose level.

With chronic exposure to boric acid in the diet, mortality at 103 weeks was ≥40 and ≥30% in male and female B6C3F1 mice, respectively, exposed to ≥79 mg boron/kg/day (≥450 mg boric acid/kg/day), compared to 18 and 34% in untreated male and female controls, respectively (NTP 1987). No clinical signs were reported for either sex; however, boron caused an increased incidence of testicular atrophy and interstitial hyperplasia in male mice exposed to doses ≥201 mg boron/kg/day (1,150 mg boric acid/kg/day).

LD_{50} values and, in some cases, the lowest levels at which death was reported in humans and animals and the duration categories are recorded in Table 3-2 and plotted in Figure 3-2.

Table 3-2 Levels of Significant Exposure to Boron - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (NS)	1 x/d				642 (LD50)	Smyth et al. 1969 BORAX	
2	Rat (NS)	1 x/d				898 (LD50)	Smyth et al. 1969 BORIC ACID	
3	Rat (Sprague-Dawley)	1 d (G)				600 F (LD50)	Weir and Fisher 1972 BORIC ACID	
4	Rat (Long- Evans)	1 d (G)				550 M (LD50)	Weir and Fisher 1972 BORIC ACID	
5	Rat (Sprague-Dawley)	1 d (G)				510 M (LD50)	Weir and Fisher 1972 BORAX	
6	Rat (Long- Evans)	1 d (G)				690 M (LD50)	Weir and Fisher 1972 BORAX	
7	Mouse (B6C3F1)	14 d (F)				2251 (20% mortality)	NTP 1987, Dieter 1994 BORIC ACID	Higher percentage mortality at higher exposure levels.

Table 3-2 Levels of Significant Exposure to Boron - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference Chemical Form	Comments
Systemic										
8	Human	3-5 d (F)	Resp				505	(vascular congestion, hemorrage in one infant who died)	Wong et al. 1964 BORIC ACID	From case-reports of 11 infants; renal, hepatic , and respiratory effects from post-mortem observations of 2 fatal cases.
			Gastro		184	(vomiting, diarrhea in infants)				
			Hepatic				505	(parenchymatous degeneration, jaundice, fatty changes, congestion in one infant who died)		
			Renal				765	(parenchymatous degeneration, reduced urine output, protein in urine in one infant who died)		
			Dermal				505	(erythema, desquamation, extensive shedding of skin in one infant who died)		
9	Mouse	14 d (F)	Gastro	926	2251	(gastric hyperplasia and dysplasia)			NTP 1987, Dieter 1994 BORIC ACID	

Table 3-2 Levels of Significant Exposure to Boron - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
10	Dog (Mongrel)	1 d (G)	Gastro		1000 (vomiting)		Weir and Fisher 1972 BORIC ACID	
Neurological								
11	Human	3-5 d (F)				505 (perivascular hemorrhage, congestion, thrombosis, and edema in brain of one infant)	Wong et al. 1964 BORIC ACID	Based on 1 fatal case report.
12	Mouse (B6C3F1)	14 d (F)		3671			NTP 1987, Dieter 1994 BORIC ACID	NOAEL is for brain histopathology.
Reproductive								
13	Rat (Wistar)	1 x/d 2 wk (G)		53 M	88 M (12 and 13% reduction in absolute and relative testes weight; increase in residual body-like structures in the testes; increase in cellular debris in the epididymal ducts; exfoliation of round spermatides, retention of step 19 spermatids)		Fukuda et al. 2000 BORIC ACID	Endpoints: male reproductive organ weights and histopathology and sperm morphology.
14	Rat (Wistar)	1 x/d 2 wk (G)		44 M	88 M (decreased stage XII spermatids and spermatogonia; increased stage X pacytene spermatocytes)		Kudo et al. 2000 BORIC ACID	Endpoints: male reproductive organ weights, histopathology, and sperm morphology.

Table 3-2 Levels of Significant Exposure to Boron - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Developmental								
15	Mouse (CD-1)	2 x/d Gd 8 (G)				70 F (reduced fetal weight and increased skeletal effects– cervical rib, rib agenesis, reduced rib length, and fused ribs)	Cherrington and Chernoff 2002 BORIC ACID	
16	Mouse (CD-1)	1 x/d Gd 8 (G)				131 F (reduced fetal weight and increased cervical ossification)	Cherrington and Chernoff 2002 BORIC ACID	
17	Mouse (CD-1)	1 x/d Gd 6-10 (G)				88 F (increased skeletal abnormalities)	Cherrington and Chernoff 2002 BORIC ACID	
18	Mouse (CD-1)	2 x/d Gd 6-8 (G)				70 F (reduced fetal weight and increased skeletal abnormalities)	Cherrington and Chernoff 2002 BORIC ACID	
19	Mouse (CD-1)	2 x/d Gd 6, 7, 9, or 10 (G)			70 F (reduced fetal weight)		Cherrington and Chernoff 2002 BORIC ACID	No skeletal abnormalities observed.

Table 3-2 Levels of Significant Exposure to Boron - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)		Reference Chemical Form	Comments
20	Mouse (CD-1)	2 x/d Gd 8 (G)				131 F	(reduced fetal weight and increased multiple skeletal malformations)	Cherrington and Chernoff 2002 BORIC ACID	
21	Mouse (CD-1)	1 x/d Gd 8-14 (G)		70 F		210 F	(no littering)	Harris et al. 1992 BORIC ACID	Endpoints: implantation sites, littering, live pups/liter, post-natal pup weight. No examination for fetal visceral or skeletal malformations.
22	Rabbit (New Zealand)	1 x/d Gd 6-19 (G)		22[b] F		44 F	(increased resorptions, decreased number of live litters and fetuses, increased fetal external, visceral, and cardiovascular malformations)	Price et al. 1996b BORIC ACID	
INTERMEDIATE EXPOSURE									
Death									
23	Rat (Sprague-Dawley)	90 d (F)				450	(100% death by 6 weeks)	Weir and Fisher 1972 BORAX	
24	Rat (Sprague-Dawley)	90 d (F)				450	(100% mortality by 6 weeks)	Weir and Fisher 1972 BORIC ACID	

Table 3-2 Levels of Significant Exposure to Boron - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
25	Mouse (B6C3F1)	13 wk (F)				577 (80% males and 60% females died)	NTP 1987, Dieter 1994 BORIC ACID	
Systemic								
26	Human	1 d/wk 7 wk (C)	Endocr	0.03 M			Ferrando and Green 1993 BORON	NOAEL is for changes in testosterone levels.
27	Rat (Sprague-Dawley)	30 d (F)	Hepatic	43 M	86 M (11% reduction in liver weight)		Dixon et al. 1979 BORAX	
			Bd Wt	172 M				
28	Rat (Fischer- 344)	9 wk (F)	Bd Wt	52 M	68 M (16% decrease in body weight gain)		Ku et al. 1993a BORIC ACID	
29	Rat (Fischer- 344)	4 wk (F)	Endocr		61 M (approximately 60-78% decrease in plasma testosterone)		Treinen and Chapin 1991 BORIC ACID	

Table 3-2 Levels of Significant Exposure to Boron - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
30	Rat (Sprague-Dawley)	90 d (F)	Cardio	450			Weir and Fisher 1972 BORAX	NOAELs are for histopathology and hematology.
			Gastro	450				
			Hemato	450				
			Musc/skel	450				
			Hepatic	45 M	150 M	(16% decrease in relative liver weight without histologic changes)		
			Renal	450				
			Dermal	45	150	(desquamated skin on paws and tails)		
			Ocular	45	150	(inflammed eyes [clinical observation])		

Table 3-2 Levels of Significant Exposure to Boron - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
31	Rat (Sprague-Dawley)	90 d (F)	Cardio	450			Weir and Fisher 1972 BORIC ACID	NOAELs are for histopathology.
			Gastro	450				
			Hemato	450				
			Musc/skel	450				
			Hepatic	45 M	150 M (22% reduction in liver weight without histologic changes)			
			Renal	450				
			Endocr	450				
			Dermal	45	150 (desquamated skin on paws and tail)			
			Ocular	45	150 (inflammed eyes [clinical observations])			

Table 3-2 Levels of Significant Exposure to Boron - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
32	Mouse (B6C3F1)	13 wk (F)	Resp	577			NTP 1987, Dieter 1994 BORIC ACID	NOAELs are for histopathology.
			Cardio	577				
			Gastro	288 M	577 M (hyperkeratosis and/or acanthosis of the stomach)			
			Hemato	35 M	72 M (splenic extramedullary hematopoiesis)			
			Hepatic	577				
			Renal	577				
			Endocr	577				
			Dermal	577				
			Bd Wt	144 M	288 M (17% reduction in body weight)	577 M (23% reduction in body weight)		

Table 3-2 Levels of Significant Exposure to Boron - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
33	Dog (Beagle)	90 d (F)	Cardio	60.5			Weir and Fisher 1972 BORAX	NOAELs are for histopathology and hematology.
			Gastro	60.5				
			Hemato	6	60.5 (decreased packed cell volume and hemoglobin values)			
			Musc/skel	60.5				
			Hepatic	60.5				
			Renal	60.5				
			Endocr	60.5				
			Dermal	60.5				
			Ocular	60.5				

Table 3-2 Levels of Significant Exposure to Boron - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
34	Dog (Beagle)	90 d (F)	Resp	60.5			Weir and Fisher 1972 BORIC ACID	NOAELs are for histopathology and hematology.
			Cardio	60.5				
			Gastro	60.5				
			Hemato	60.5				
			Musc/skel	60.5				
			Hepatic	6 F	60.5 F (46% increase in relative liver weight with no adverse histologic changes)			
			Renal	60.5				
			Endocr	60.5				
			Dermal	60.5				
			Ocular	60.5				
Neurological								
35	Rat (Sprague-Dawley)	90 d (F)		50 F	170 F (15% increase in relative brain weight)		Weir and Fisher 1972 BORAX	
36	Rat (Sprague-Dawley)	90 d (F)		50 F	170 F (15% increase in relative brain weight)		Weir and Fisher 1972 BORIC ACID	
37	Mouse (B6C3F1)	13 wk (F)		577			NTP 1987, Dieter 1994 BORIC ACID	NOAEL is for brain histopathology.

Table 3-2 Levels of Significant Exposure to Boron - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
38	Dog (Beagle)	90 d (F)		60.5 F			Weir and Fisher 1972 BORAX	
Reproductive								
39	Rat (Sprague-Dawley)	90 d (W)		0.6			Dixon et al. 1976 BORAX	NOAEL is for reproductive organ weights and histopathology.
40	Rat (Sprague-Dawley)	30 d (F)			43 M (decreased testicular enzyme activities; increased plasma FSH)	86 M (infertility for 3 weeks following exposure)	Dixon et al. 1979 BORAX	Endpoints: body and organ weights, testicular enzyme activities, testicular histopathology, ability to impregnate non-treated females.
41	Rat (Sprague-Dawley)	60 d (F)			43 M (62% decrease in testes weight; 37% decrease in epidiymis weight; increased plasma FSH; reduced diameter of seminiferous tubules)	86 M (infertility for 5 weeks following exposure)	Dixon et al. 1979 BORAX	Endpoints: body and organ weights, testicular enzyme activities, testicular histopathology, ability to impregnate non-treated females.

Table 3-2 Levels of Significant Exposure to Boron - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
42	Rat (Wistar)	1 x/d 4 wk (G)				53 M (13 and 15% reduction in absolute and relative testes weight; cellular debris in the testes, cauda and caput epididymis; focal atrophy of the seminiferous tubules; decrease in the number of sperm in the ducta lumina)	Fukuda et al. 2000 BORIC ACID	Endpoints: male reproductive organ weights and histopathology.
43	Rat (Fischer- 344)	9 wk (F)			26 M (milky inhibited spermiation by week 5)	52 M (testicular atrophy by week 9; severe inhibition of spermiation)	Ku et al. 1993a BORIC ACID	Endpoints: male reproductive organ weights and histopathology, sperm morphology.
44	Rat (Wistar)	1 x/d 4 wk (G)		22 M	44 M (reduced sperm motility; reduced total sperm in caudal epididymis)		Kudo et al. 2000 BORIC ACID	Endpoints: male reproductive organ weights, histopathology, and sperm morphology.

Table 3-2 Levels of Significant Exposure to Boron - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
45	Rat	30-60 d (F)		50		100 (testicular atrophy, decreased enzymes)	Lee et al. 1978 BORAX	
46	Rat (Sprague-Dawley)	60 d (F)				136 M (decreased weights of testes and associated tissues; decreased sperm motility, number of spermatocytes, spermatids, Leydig cells, testosterone levels, sexually aggressive behavior, number of females impregnated; increased fetal resorption in impregnated females)	Nusier and Bataineh 2005 BORIC ACID	Endpoints: male reproductive organ weights, histopathology, sperm morphology, plasma FSH and testosterone levels, sexual behavior.
47	Rat (Long- Evans)	70 d (W)			44.7 M (impaired spermatogenesis)		Seal and Weeth 1980 BORAX	
48	Rat (Sprague-Dawley)	90 d (F)		45 M	150 M (53% reduction in testicular weight)		Weir and Fisher 1972 BORAX	
49	Rat (Sprague-Dawley)	90 d (F)		45 M		150 M (53% decrease in testicular weight; testicular atrophy)	Weir and Fisher 1972 BORAX	

Table 3-2 Levels of Significant Exposure to Boron - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
50	Rat (Sprague-Dawley)	3 gen (F)		30		101[c] M (complete sterility) 116 F (complete sterility)	Weir and Fisher 1972 BORAX	Both genders exposed. Sterility associated with testicular atrophy in males and decreased ovulation in females.
51	Rat (Sprague-Dawley)	3 gen (F)		30		101[c] M (complete sterility) 116 F (complete sterility)	Weir and Fisher 1972 BORIC ACID	Both genders exposed. Sterility associated with testicular atrophy in males and decreased ovulation in females.
52	Rat (Sprague-Dawley)	3 gen (F)				116 F (complete sterility)	Weir and Fisher 1972 BORAX	Exposed females mated with non-exposed males; females showed decreased ovulation.
53	Rat (Sprague-Dawley)	3 gen (F)				116 F (complete sterility)	Weir and Fisher 1972 BORIC ACID	Exposed females mated with non-exposed males; females showed decreased ovulation.

Table 3-2 Levels of Significant Exposure to Boron - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
54	Rat (Wistar)	3 wk (G)		9 M		26 M (increased pre-implantation fetal loss; decreased sperm motility; morphologically-abnormal sperm heads and tails)	Yoshizaki et al. 1999 BORIC ACID	Exposed males mated with unexposed females; inability to impregnate females at 88 mg/kg/day.
55	Mouse (CD-1)	27 wk (F)		27 M		111 M (degeneration of the seminiferous tubules; impaired spermatogenesis; decreased sperm motility, litters per mating pair, and live pups per litter)	Fail et al. 1991 BORIC ACID	Treated males mated with untreated females. Complete sterility at 221 mg boron/kg/day.
56	Mouse (CD-1)	M: 17 d (d 3-20) F: 20 d (d 0-20) (G)		21 M	70 M (reduced testis weight, germ cell loss)	210 M (exfoliation/disruption of seminiferous tubules; inhibited spermiation; no effect on % females pregnant)	Harris et al. 1992 BORIC ACID	Mating on days 8-12; Endpoints: male reproductive organ weight and histology; % pregnant and number of live implants.
57	Mouse (B6C3F1)	13 wk (F)				288 M (degeneration or atrophy of seminiferous tubules)	NTP 1987, Dieter 1994 BORIC ACID	

Table 3-2 Levels of Significant Exposure to Boron - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
58	Dog (Beagle)	90 d (F)		6 M		60.5 M (50% decrease in relative testes weight; severe testicular atrophy)	Weir and Fisher 1972 BORAX	
59	Dog (Beagle)	90 d (F)		6 M		60.5 M (40% decrease in testes weight; severe testicular atrophy)	Weir and Fisher 1972 BORIC ACID	
Developmental								
60	Rat (Sprague-Dawley)	Gd 0-20 (F)			13.6[d] (reduced fetal weight)	28.4 (rib cage defects, enlargement of the lateral ventricles of the brain, increased resorptions)	Heindel et al. 1992 BORIC ACID	
61	Rat (Sprague-Dawley)	Gd 0-20 (F)		10 F	13 F[d] (reduced fetal weight, increase in skeletal abnormalities observed on gestation day 20)		Price et al. 1996a, 1998 BORIC ACID	Effects seen on gestation day 20 were not observed on postnatal day 21.
62	Mouse (CD-1)	Gd 0-17 (F)		43.4	79 (reduced fetal body weight)	175.3 (increased skeletal effects [short rib XIII, fused ribs, agenesis of lumbar vertabra], increased resorptions)	Heindel et al. 1992 BORIC ACID	

Table 3-2 Levels of Significant Exposure to Boron - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
CHRONIC EXPOSURE								
Death								
63	Mouse (B6C3F1)	103 wk (F)				79 (40% mortality)	NTP 1987, Dieter 1994 BORIC ACID	
Systemic								
64	Rat (Sprague-Dawley)	2 yr (F)	Resp	81			Weir and Fisher 1972 BORIC ACID	NOAELs are for histopathology.
			Cardio	81				
			Gastro	81				
			Hemato	24 F	81 F (decreased packed cell volume and hemoglobin levels)			
			Hepatic	81				
			Renal	81				
			Endocr	81				
			Dermal	24	81 (scaly tails, desquamation of skin on footpads)			
			Ocular	24	81 (bloody ocular discharge)			
			Bd Wt	24	81 (reduced growth throughout study)			

Table 3-2 Levels of Significant Exposure to Boron - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
65	Rat (Sprague-Dawley)	2 yr (F)	Resp	81			Weir and Fisher 1972 BORAX	NOAELs are for histopathology.
			Cardio	81				
			Gastro	81				
			Hemato	24	81 (decreased packed cell volume and hemoglobin levels)			
			Hepatic	81				
			Renal	81				
			Endocr	81				
			Dermal	24	81 (scaly tails, desquamation of skin on footpads)			
			Ocular	24	81 (bloody ocular discharge)			
			Bd Wt	24	81 (decreased growth throughout study)			

Table 3-2 Levels of Significant Exposure to Boron - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
66	Mouse (B6C3F1)	103 wk (F)	Resp	79 F		201 F (lung hemorrhage)	NTP 1987, Dieter 1994 BORIC ACID	NOAELs are for histopathology.
			Cardio	201				
			Gastro	201				
			Hemato		79 M (spenic hematopoiesis)			
			Hepatic		79 (chronic inflammation; coagulative necrosis)			
			Renal	201				
			Endocr	201				
			Ocular	201				
			Bd Wt	79	201 (10%-17% decrease in body weight)			

Table 3-2 Levels of Significant Exposure to Boron - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
67	Dog (Beagle)	2 yr (F)	Resp	6.8			Weir and Fisher 1972 BORIC ACID	NOAELs are for histopathology.
			Cardio	6.8				
			Gastro	6.8				
			Hemato	6.8				
			Musc/skel	6.8				
			Hepatic	6.8				
			Renal	6.8				
			Endocr	6.8				
			Dermal	6.8				
			Ocular	6.8				
			Bd Wt	6.8				

Table 3-2 Levels of Significant Exposure to Boron - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
68	Dog (Beagle)	2 yr (F)	Resp	6.8			Weir and Fisher 1972 BORAX	NOAELs are for histopathology.
			Cardio	6.8				
			Gastro	6.8				
			Hemato	6.8				
			Musc/skel	6.8				
			Hepatic	6.8				
			Renal	6.8				
			Endocr	6.8				
			Dermal	6.8				
			Ocular	6.8				
			Bd Wt	6.8				
Neurological								
69	Rat (Sprague-Dawley)	2 yr (F)		24	81 (increased relative brain weight)		Weir and Fisher 1972 BORIC ACID	
70	Rat (Sprague-Dawley)	2 yr (F)		24	81 (increased relative brain weight)		Weir and Fisher 1972 BORAX	

Table 3-2 Levels of Significant Exposure to Boron - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
71	Mouse (B6C3F1)	103 wk (F)		201			NTP 1987, Dieter 1994 BORIC ACID	NOAEL is for brain histopathology.
Reproductive								
72	Rat (Sprague-Dawley)	2 yr (F)		24 M		81 M (decreased relative testes weight; testicular atrophy; atrophied seminiferous epithelium and reduced tubular size)	Weir and Fisher 1972 BORAX	
73	Rat (Sprague-Dawley)	2 yr (F)		24 M		81 M (decreased relative testes weight; testicular atrophy; atrophied seminiferous epithelium and reduced tubular size)	Weir and Fisher 1972 BORIC ACID	
74	Mouse (B6C3F1)	103 wk (F)		79		201 (testicular atrophy, interstitial hyperplasia)	NTP 1987, Dieter 1994 BORIC ACID	
75	Dog (Beagle)	2 yr (F)		6.8 M			Weir and Fisher 1972 BORAX	

Table 3-2 Levels of Significant Exposure to Boron - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
76	Dog (Beagle)	2 yr (F)		6.8 M			Weir and Fisher 1972 BORIC ACID	

a The number corresponds to entries in Figure 3-2.

b Used to derive an acute-duration oral MRL of 0.2 mg/kg/day; dose divided by an uncertainty factor of 100 (10 for interspecies extrapolation and 10 for human variability).

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

d Used to derive an intermediate-duration oral MRL of 0.2 mg/kg/day; a point of departure from benchmark dose analysis of 10.3 mg boron/kg/day was divided by a chemical-specific uncertainty factor of 66 (3.3 for toxicokinetic extrapolation from animals to humans, 3.16 for toxicodynamic extrapolation from animals to humans, 2.0 for variability in human toxicokinetics, and 3.16 for variability in human toxicodynamics).

Bd Wt = body weight; (C) = capsule; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; (F) = feed; F = Female; FSH = follicle stimulating hormone; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; Hemato = hematological; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; Metab = metabolic; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; x = time(s); (W) = drinking water; wk = week(s); yr = year(s)

Figure 3-2 Levels of Significant Exposure to Boron - Oral

Acute (≤14 days)

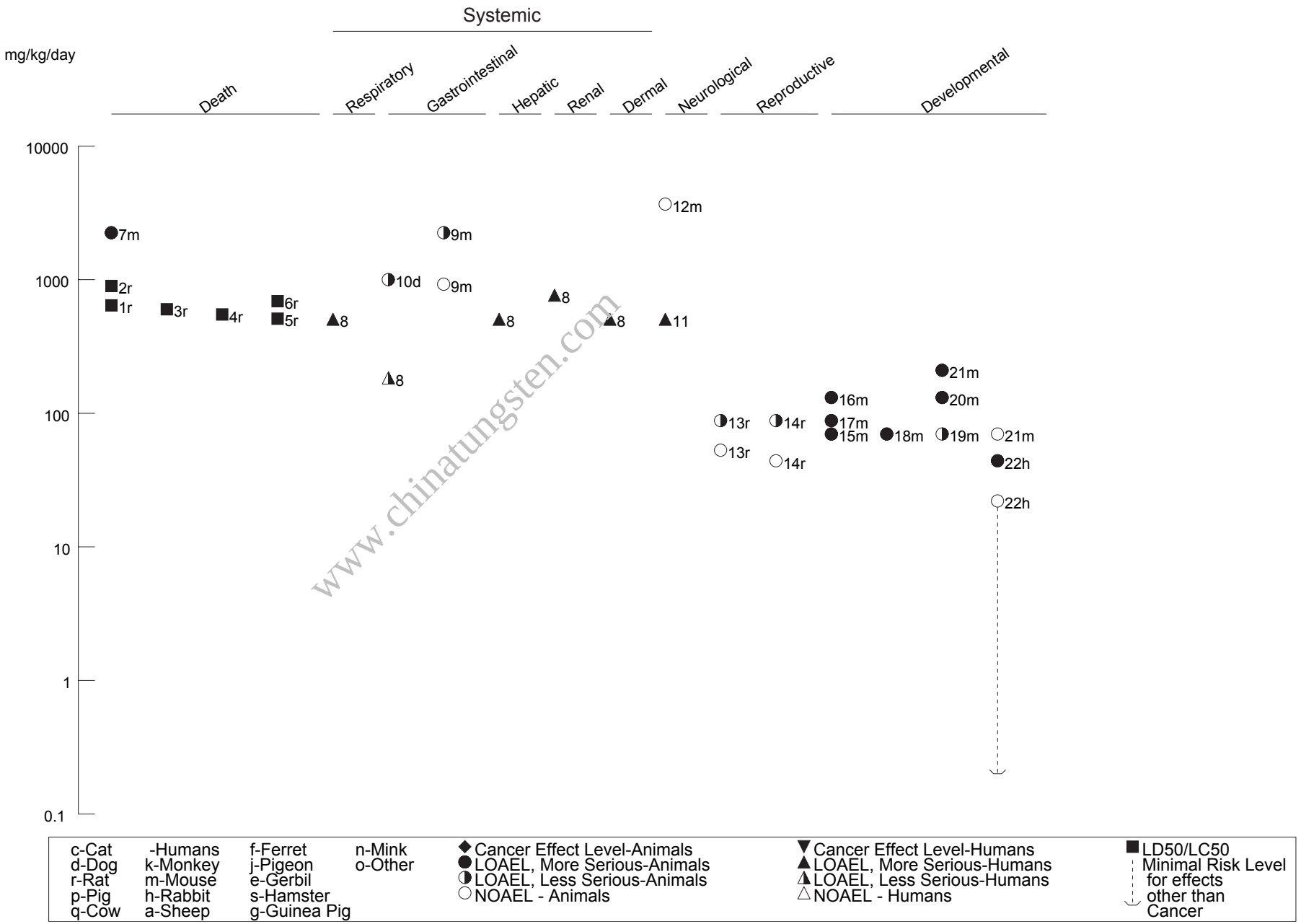


Figure 3-2 Levels of Significant Exposure to Boron - Oral *(Continued)*

Intermediate (15-364 days)

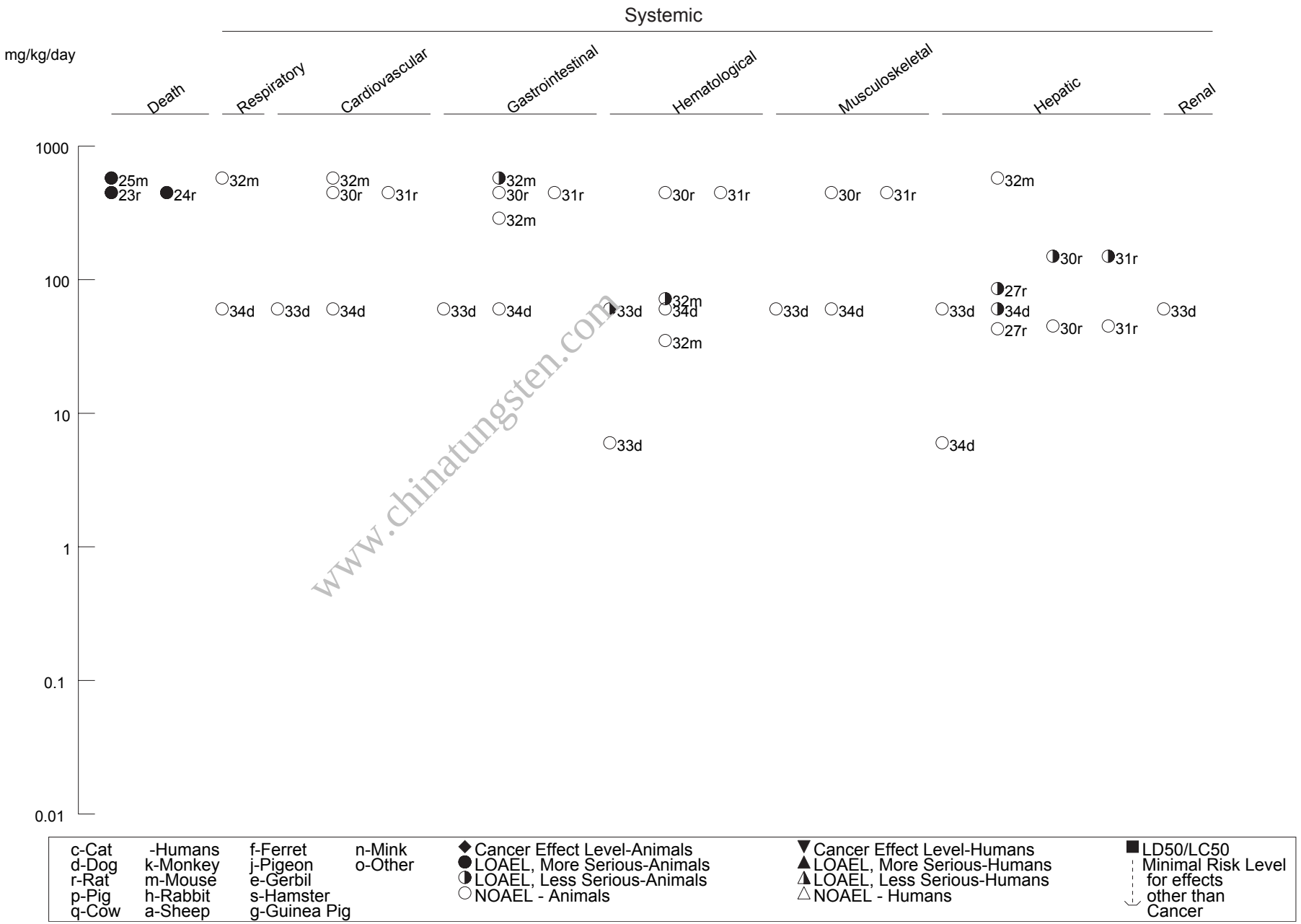


Figure 3-2 Levels of Significant Exposure to Boron - Oral *(Continued)*

Intermediate (15-364 days)

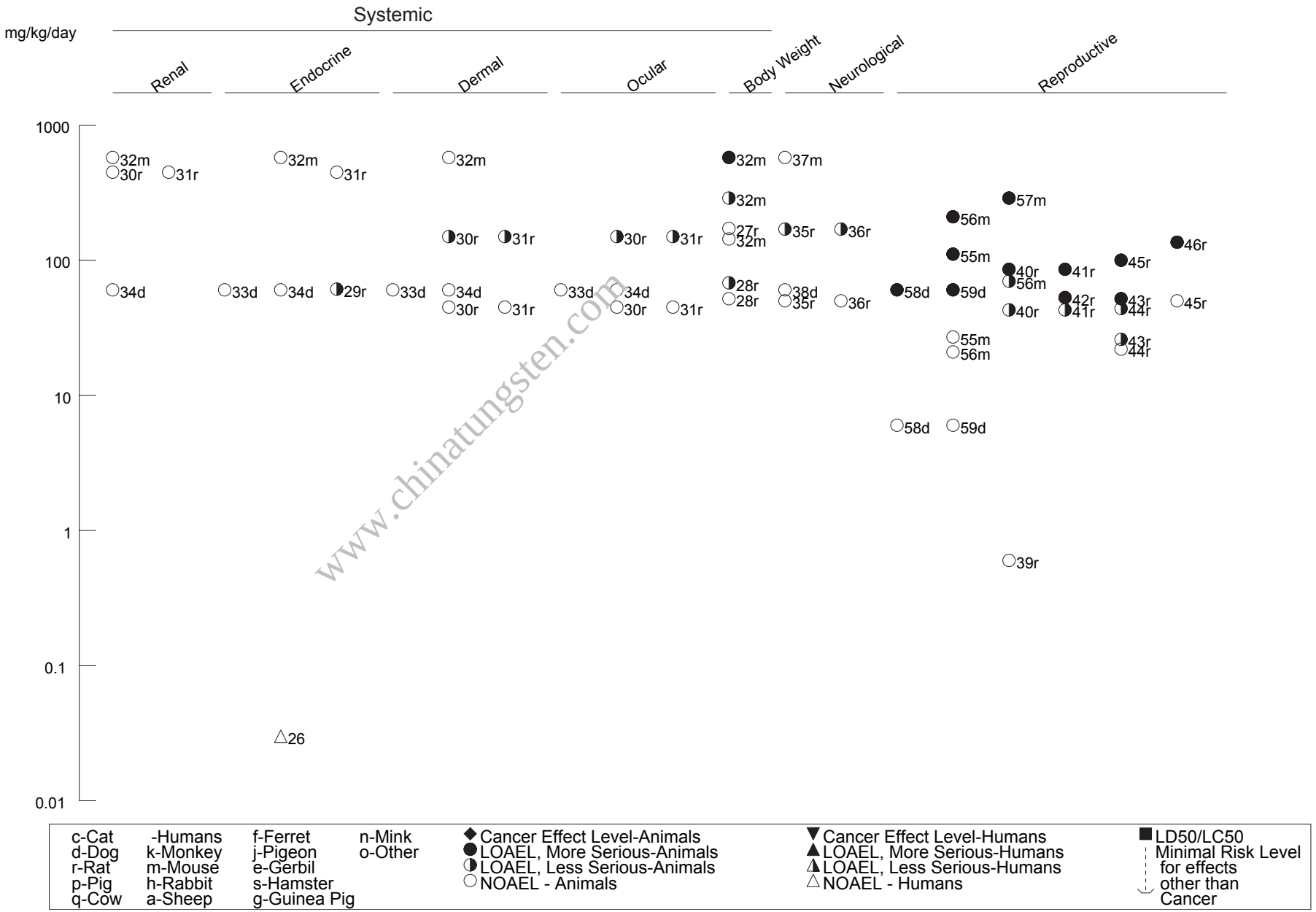


Figure 3-2 Levels of Significant Exposure to Boron - Oral *(Continued)*

Intermediate (15-364 days)

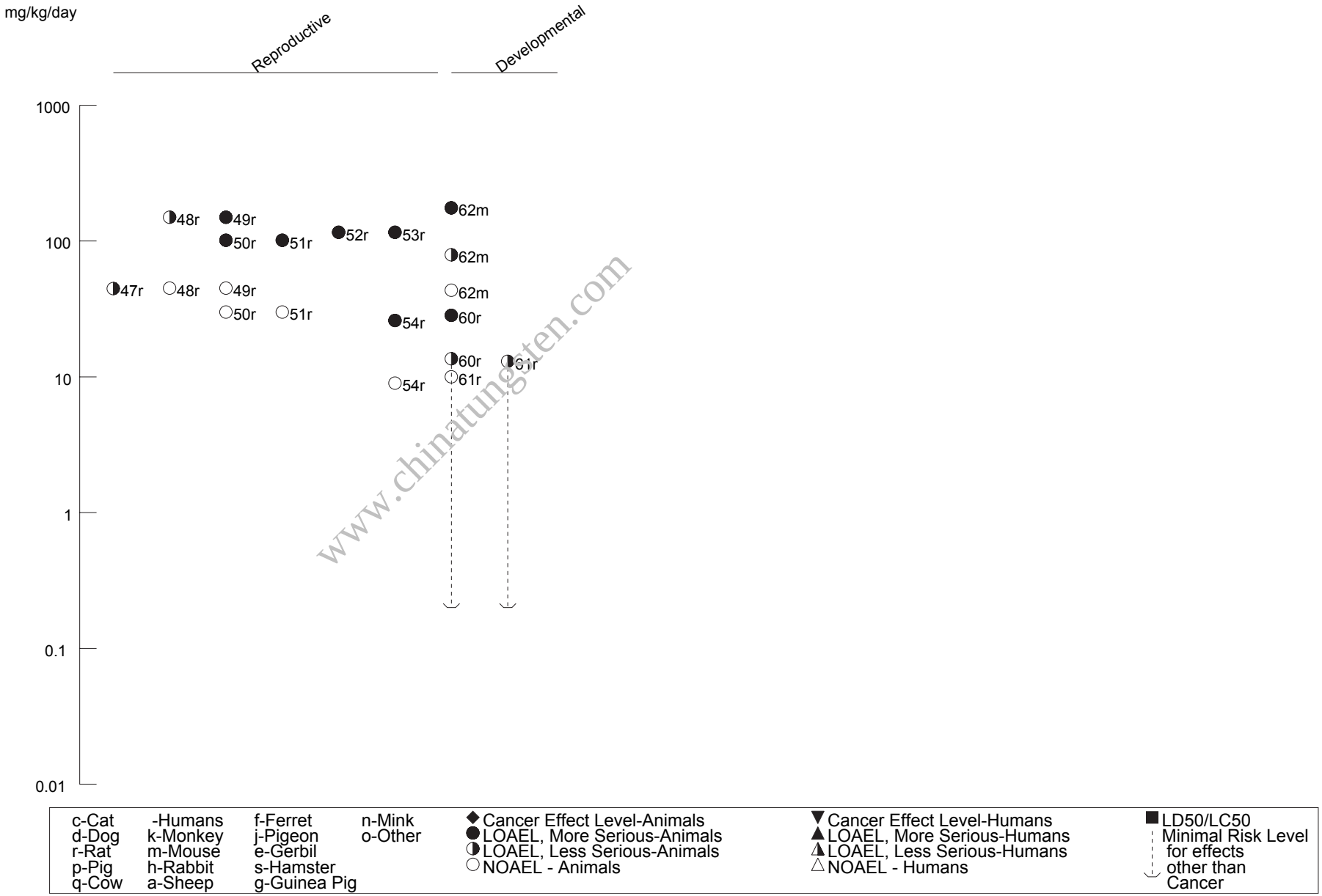


Figure 3-2 Levels of Significant Exposure to Boron - Oral *(Continued)*

Chronic (≥365 days)

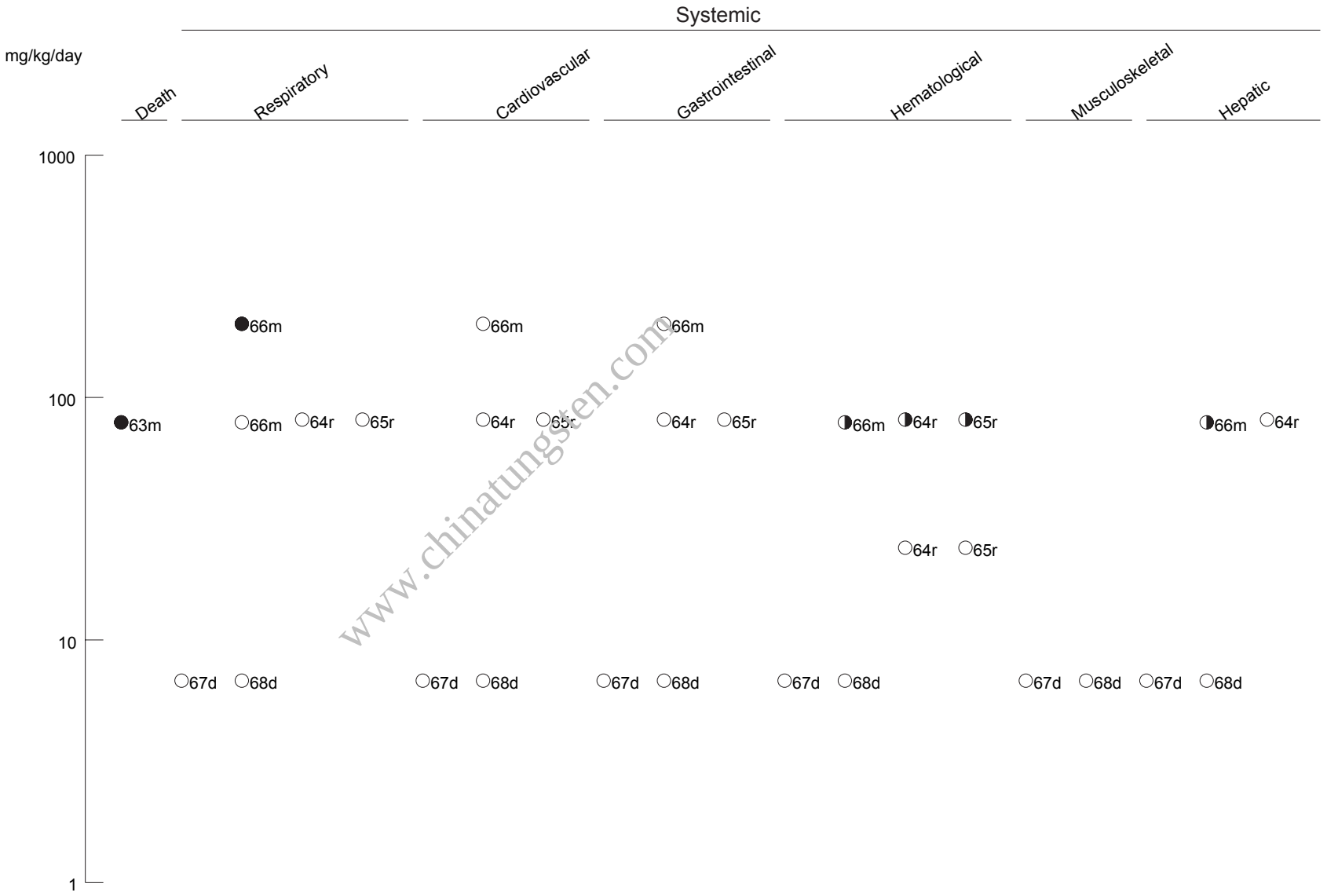


Figure 3-2 Levels of Significant Exposure to Boron - Oral *(Continued)*

Chronic (≥365 days)

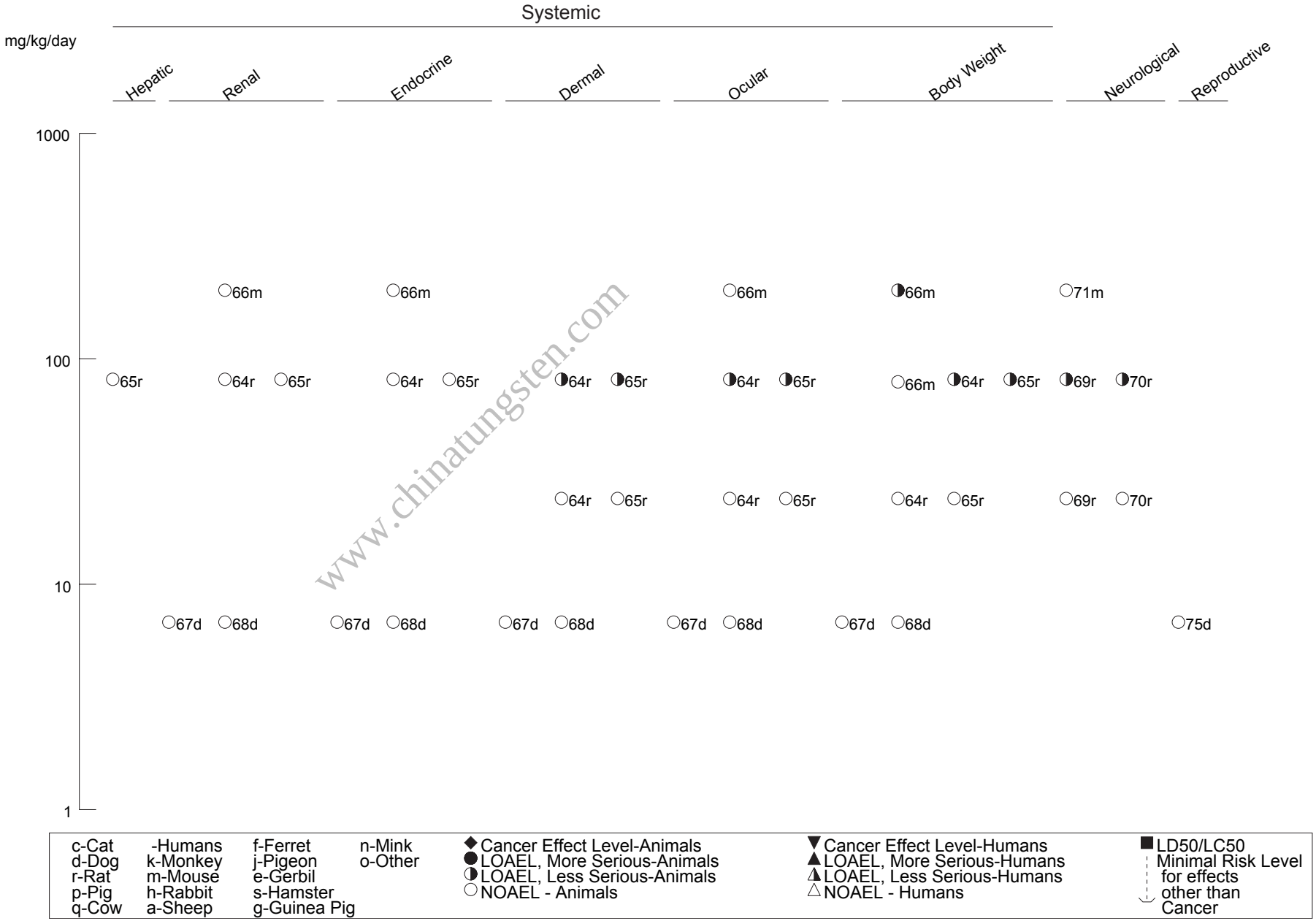
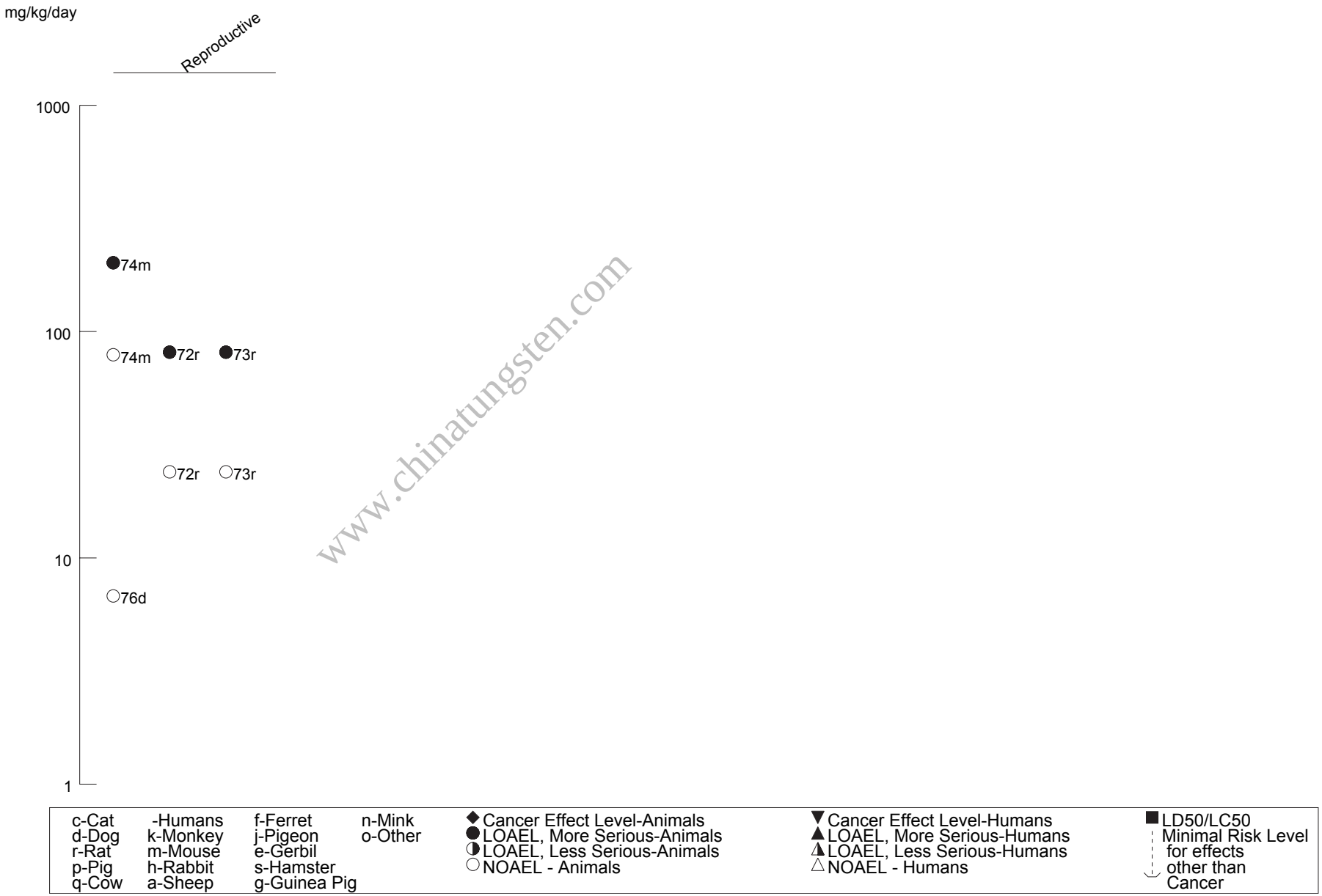


Figure 3-2 Levels of Significant Exposure to Boron - Oral *(Continued)*

Chronic (≥365 days)



3.2.2.2 Systemic Effects

No studies were located regarding respiratory effects in animals or musculoskeletal effects in humans or animals after oral exposure to boron.

Information on respiratory, gastrointestinal, hematological, cardiovascular, hepatic, renal, and dermal/ocular effects is discussed below. The highest NOAEL values and all reliable LOAEL values for these systemic effects for each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

Respiratory Effects. Widespread vascular congestion and hemorrhages in the lungs were reported in one infant who ingested an estimated dose of 505 mg boron/kg/day for 3–5 days (Wong et al. 1964).

Cardiovascular Effects. Ingestion of 85 mg boron/kg (as 30 g of boric acid) by a 77-year-old man (Ishii et al. 1993) resulted in cardiopulmonary hypotension and death from cardiac insufficiency.

Gastrointestinal Effects. Ingestion of boron in humans can cause gastrointestinal effects. Nausea, persistent vomiting, diarrhea, and colicky abdominal pain in infants were associated with acute ingestion of a total of ≥184 mg boron/kg/day (based on 1.9 kg body weight) as boric acid, which was accidentally incorporated in infant formula (Wong et al. 1964). Vomiting and diarrhea occurred following ingestion of 85 mg boron/kg (as 30g of boric acid) by a 77-year-old man (Ishii et al. 1993). Vomiting was the only sign of boron toxicity in two adult females who ingested 14 g boron (80 g boric acid) in a fungicide and 52 g boron (297 g boric acid) in a suicide attempt. In the absence of body weight data, doses for these cases could not be estimated. The subjects were hospitalized for 24–96 hours and did not develop further symptoms following release (Linden et al. 1986). Food poisoning of 13 children with unknown levels of aflatoxin and boric acid (Chao et al. 1991a, 1991b) resulted in vomiting, diarrhea, abdominal pain, anorexia, and upper gastrointestinal erosion.

In B6C3F1 mice, dietary exposure to ≥2,251 mg boron/kg/day as boric acid for 14 days resulted in gastric hyperplasia and dysplasia (NTP 1987). Dogs given a single dose of 1,000 mg boron/kg as boric acid vomited (Weir and Fisher 1972).

Hematological Effects. In animals orally exposed for intermediate or chronic durations, effects on hematological end points have been observed sporadically in dogs and consistently in mice; they did not occur in rats exposed for 90 days. Mongrel dogs fed 60.5 mg boron/kg/day for 90 days in the diet as borax (but not as boric acid) had decreased packed cell volume and hemoglobin values, but no hematological effects were seen in dogs fed 81 mg boron/kg/day as borax or boric acid for 2 years (Weir and Fisher 1972). Erythrocyte count and total and differential leukocyte counts were comparable to control levels (Weir and Fisher 1972). Splenic extramedullary hematopoiesis occurred in mice fed 72 mg boron/kg/day as boric acid for 90 days and 79 mg boron/kg/day for 2 years (Dieter 1994; NTP 1987), while no hematological effects were observed in rats fed 450 mg boron/kg/day as borax or boric acid for 90 days (Weir and Fisher 1972). Decreased packed cell volume and hemoglobin values were seen in rats fed 81 mg boron/kg/day as borax for 2 years (Weir and Fisher 1972).

Hepatic Effects. Case reports in humans suggest that the liver is susceptible to boron toxicity at high dose levels (Wong et al. 1964). Jaundice has been reported, and there were mild alterations at histological examination in infants who ingested 505 or 765 mg boron/kg/day as boric acid (accidentally incorporated in infant formula) for 3–5 days (Wong et al. 1964). In the same incident, congestion and fatty changes were observed, and there was parenchymatous degeneration in newborn infants who ingested 505 or 765 mg boron/kg as boric acid for 3–5 days (Wong et al. 1964). Coagulative necrosis of the liver, proliferative metaplasia of the hepatocytes, giant cell formation, central vein sclerosis, bile stasis, and hepatic steatosis were observed in children ingesting unknown levels of aflatoxin and boric acid in Chinese noodles (Chao et al. 1991a, 1991b).

In mice, the liver appears to be a toxicity target of repeated oral exposure to boric acid, but it is not a target in rats and dogs repeatedly exposed to boric acid or borates. Two-year dietary exposures of ≥79 mg boron/kg/day as boric acid to B6C3F1 mice resulted in chronic inflammation and coagulative necrosis in the liver (NTP 1987; Dieter 1994), but no exposure-related hepatic lesions were found in Sprague-Dawley rats fed 81 mg boron/kg/day as boric acid or borax in the diet for 2 years or in mongrel dogs fed 6.8 mg boron/kg/day as boric acid or borax in the diet for 2 years (Weir and Fisher 1972). No exposure-related liver lesions were seen in mice fed 577 mg boron/kg/day as boric acid for 13 weeks (Dieter 1994; NTP 1987); in Sprague-Dawley rats fed 450 mg boron/kg/day as boric acid or borax for 90 days (Weir and Fisher 1972); or in mongrel dogs fed 60.5 mg boron/kg/day as boric acid or borax for 90 days (Weir and Fisher 1972).

Boron-related changes in liver weights have not been consistently observed in animal studies. Reduced liver weights were observed in rats fed 86 mg boron/kg/day as borax for 30 days (Dixon et al. 1979) and fed 150 mg boron/kg/day as borax or boric acid for 90 days (Weir and Fisher 1972), while increased relative liver weights were seen in mongrel dogs fed 60.5 mg boron/kg/day as boric acid for 90 days (Weir and Fisher 1972).

In liver microsomal fractions from rats given approximately 20.8 mg boron/kg/day as borax in drinking water, NADPH-cytochrome C reductase activity and cytochrome b5 content decreased in the liver microsomal fraction after 10 and 14 weeks of exposure (Settimi et al. 1982). There was also a reduction in the cytochrome P-450 concentration detected at 14 weeks (Settimi et al. 1982). The toxicological significance of these biochemical changes is not clear, especially since intermediate- and chronic-duration feeding studies with Sprague-Dawley rats fed boric acid or borax did not report exposure-related hepatic lesions (Weir and Fisher 1972).

Renal Effects. Human case reports involving high accidental ingestion levels show that boron can cause injury to the kidney. Acute renal failure was observed in a 77-year-old man ingesting 85 mg boron/kg (as 30 g of boric acid) (Ishii et al. 1993). Degenerative changes in parenchymal cells with oliguria and albuminuria have been demonstrated in two newborn infants after ingestion of 505 and 765 mg boron/kg/day as boric acid in an evaporated milk formula over a period of 3–5 days (Wong et al. 1964). Acute renal tubule necrosis was seen in children dying from ingestion of unknown levels of aflatoxin and boric acid in Chinese noodles (Chao et al. 1991a, 1991b).

No exposure-related renal lesions were observed in Sprague-Dawley rats fed up to 450 mg boron/kg/day as borax or boric acid for 90 days (Weir and Fisher 1972), in mice fed 577 mg boron/kg/day as boric acid for 13 weeks (NTP 1987; Dieter 1994), or in dogs fed up to 60.5 mg boron/kg/day as borax or boric acid for 90 days (Weir and Fisher 1972). With 2 years of dietary exposure, no exposure-related renal lesions were observed in Sprague-Dawley rats fed 81 mg boron/kg/day as borax or boric acid (Weir and Fisher 1972), in B6C3F1 mice fed up to 201 mg boron/kg/day as boric acid (Dieter 1994; NTP 1987), or in mongrel dogs fed 6.8 mg boron/kg/day as borax or boric acid (Weir and Fisher 1972). The available data indicate that the kidney is not a sensitive toxicity target of oral exposure to boric acid or borates.

Endocrine Effects. Human data for endocrine effects from orally ingested boron are limited to studies of low-dose boron nutritional supplementation. Postmenopausal women ingesting 0.4 mg boron/day (as 3.25 mg sodium borate/day) in the diet had a 3-fold increase in plasma testosterone levels

compared to those ingesting 0.03 mg boron/day (as 0.25 mg sodium borate/day) (Nielsen et al. 1987). However, bodybuilders taking daily supplements of 2.5 mg boron (approximately 0.03 mg/kg; calculated using mean body weights from study data) for 7 weeks did not exhibit differences from controls in free or total plasma testosterone levels (Ferrando and Green 1993).

Rats fed diets with 61 mg boron/kg/day as boric acid (9000 ppm) for 28 days had decreases of approximately 60–78% in plasma testosterone levels beginning on day 4 of exposure (Treinen and Chapin 1991). Follicle stimulating hormone (FSH) and leutenizing hormone (LH) levels in the blood of rats fed 26–68 mg boron/kg/day as boric acid (3,000–9,000 ppm; doses estimated by study authors) in the diet were increased, possibly in response to testicular atrophy observed in the 52 and 68 mg boron/kg/day groups (Ku et al. 1993a). No histologic lesions were observed in thyroid, adrenals, or pituitary tissues of Sprague-Dawley rats fed 450 or 81 mg boron/kg/day as boric acid or borax in the diet for 90 days or 2 years, respectively, or in mongrel dogs fed 60.5 or 6.8 mg boron/kg/day as boric acid or borax in the diet for 90 days or 2 years, respectively (Weir and Fisher 1972) or in pituitary tissues of mice fed 577 or 201 mg boron/kg day as boric acid for 90 days or 2 years, respectively (Dieter 1994; NTP 1987).

Dermal Effects. Skin effects can occur following ingestion of boron (as boric acid) in humans. Extensive exfoliative dermatitis began in infants as an erythema involving palms, soles, and buttocks. It eventually became generalized with subsequent bulbous formation, massive desquamation, and sloughing (Wong et al. 1964). These changes were associated with ingestion of 505 mg boron/kg/day; however, skin lesions were lacking following ingestion of 765 mg boron/kg/day. Similarly, extensive erythema with desquamation was observed in an adult who ingested single doses of boric acid powder (Schillinger et al. 1982). The exact amount ingested was not stated. However, 14 g (equivalent to 22.5 mg boron/kg based on 109 kg body weight) was measured as missing from a container from which the patient admitted consuming half its contents.

In animals studies, skin lesions were observed in Sprague-Dawley rats fed 150 mg boron/kg/day as borax or boric acid in the diet for 90 days (skin desquamations on the paws and tails) or 81 mg boron/kg/day for 2 years (scaly tails and desquamation on footpads) (Weir and Fisher 1972), but dermal lesions were not observed in B6C3F1 mice exposed to boric acid in the diet for 13 weeks or 2 years (Dieter 1994; NTP 1987) or in mongrel dogs exposed to boric acid or borax in the diet for 90 days or 2 years (Weir and Fisher 1972).

Ocular Effects. There are no reports of ocular effects in humans following oral exposure to humans.

Sprague-Dawley rats fed 150 mg boron/kg/day as borax or boric acid for 90 days exhibited inflammation of the eyes, while 81 mg boron/kg/day as borax or boric acid in the diet for 2 years resulted in bloody ocular discharge (Weir and Fisher 1972). No ocular effects were seen in dogs fed 60.5 mg boron/kg/day as borax or boric acid for 90 days or 6.8 mg boron/kg/day borax or boric acid for 2 years (Weir and Fisher 1972). Likewise, mice fed 201 mg boron/kg/day as boric acid for 2 years exhibited no ocular effects.

Body Weight Effects. Fisher 344 rats fed 68 mg boron/kg/day as boric acid (9,000 ppm) for 9 weeks had 6% lower body weight gain than controls (Ku et al. 1993a). Male and female B6C3F1 mice fed 288 and 577 mg boron/kg/day as boric acid (0.5% of diet) for 13 weeks had 17 and 23% decreased weight gains, respectively, while 2-year exposures to 201 mg boron/kg/day as boric acid resulted in 19% lower weight gains in both sexes (NTP 1987, Dieter 1994).

3.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans or animals after oral exposure to boron.

3.2.2.4 Neurological Effects

Case reports in humans have indicated neurological effects after accidental ingestion of high levels of boron (as boric acid). Newborn infants who ingested 4.5–14 g boric acid showed central nervous system involvement manifested by headache, tremors, restlessness, and convulsions followed by weakness and coma (Wong et al. 1964). Histological examination of 2 of 11 infants revealed congestion and edema of brain and meninges with perivascular hemorrhage and intravascular thrombosis at a dose ≥505 mg boron/kg/day (Wong et al. 1964). Seizure disorders have been associated with boron exposures (as borax) in infants who ingested 12–120 g borax for 4–10 weeks (O'Sullivan and Taylor 1983) and 9–125 g borax over a period of 5–12 weeks (Gordon et al. 1973). Estimates of boron dose could not be determined since the authors did not provide body weight data. Blood boron levels in the infants exposed who ingested borax ranged from 2.6 to 8.5 µg/mL (O'Sullivan and Taylor 1983). In one infant with a seizure disorder who ingested (via pacifier dipped in honey and borax mixture) approximately 125 g borax over 3 months, the blood boron level was 1.64 mg/100 mL (Gordon et al. 1973).

Existing animal studies do not provide evidence that the neurological system is a toxicity target of repeated oral exposure to boric acid or borates, but no studies have examined batteries of neurological end points in animals following exposure to boron compounds. Relative brain weights were increased in mongrel dogs fed 60.5 mg boron/kg/day as borax, but not boric acid, for 90 days and in rats fed 170 or 81 mg boron/kg/day as borax or boric acid for 90 days or 2 years, respectively (Weir and Fisher 1972). No histological lesions were observed in these animals or in the brain or spinal cord of mice fed 577 or 201 mg boron/kg/day as boric acid for 13 weeks or 2 years, respectively (NTP 1987; Dieter 1994).

In Wistar rats, exposure to approximately 20.8 mg boron/kg/day as borax (based on weight of 0.35 kg and average water consumption of 20.7 mL) in drinking water for up to 14 weeks caused increased cerebral succinate dehydrogenase activity after 10 and 14 weeks of exposure (Settimi et al. 1982). Increased ribonucleic acid (RNA) concentration and increased acid proteinase activity in brain occurred after 14 weeks (Settimi et al. 1982). The neurological significance of these biochemical changes is unclear.

All LOAEL values for neurological effects in humans and animals are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.5 Reproductive Effects

A survey of Turkish subpopulations compared fertility rates of 1,068 families living in two Turkish villages having drinking water boron levels of 2–29 mg/liter (from nearby geological deposits of calcium borate) with 610 families living in three other villages having drinking water boron levels of 0.03–0.4 mg/liter (Sayli 1998a, 1998b; Sayli et al. 1998). Assuming 70-kg body weights and 2-L/day drinking water consumption, these boron levels would results in an estimated range of daily doses of 0.06–0.8 mg/kg/day. Three generations of families were represented. No significant differences in frequencies of infertility were observed between high- (2.34% infertility) and low-exposure (2.62% infertility) village groups. A separate analysis of the same subpopulation found no association of higher drinking water borate concentrations with increased rates of spontaneous abortions, stillbirths, or infant death (Tuccar et al. 1998). A follow-up study of this population reported no significant differences in infertility frequencies between the two populations (Sayli 2003).

A questionnaire was administered to 542 male workers at a borax and boric acid production facility in California inquiring about the ability to conceive a child after at least 9 months of employment at the facility (Whorton et al. 1994). The worker population was categorized as having low, mid, or high

exposures to borax or boric acid (exposure levels were not reported). A standardized birth ratio (SBR) was calculated as the number of children born to wives compared to the number of births expected in the same fraction of the U.S. population. The calculated SBR of 113 indicated higher birth rates among the borate workers relative to the U.S. population. Thus, this survey provided no evidence for association between occupational exposure to borax or boric acid and impaired fertility; however, the study is limited by non-rigorous survey design, lack of quantitative exposure data, and lack of a comparable comparison (control) group.

A cross-sectional survey of 1,187 Chinese boron mining and processing workers examined the association of boron exposure and various lifestyle factors to multiple reproductive indices (Chang et al. 2006). No exposure estimates were reported, but boron levels in drinking water and staple foodstuffs were significantly higher for surveyed workers compared to a comparison population. After correcting for age, race, diet, alcohol consumption, smoking, and education, there were no statistically significant differences between workers and the comparison population for ability to sire offspring, delayed pregnancy, multiple births, miscarriages, induced abortions, stillbirths, or tubal or ectopic pregnancies.

While the human survey database is extensive in that large populations were sampled from multiple locations over a chronic exposure duration, they are limited for informing dose response relationships for reproductive effects. Specifically, the reliance on questionnaires and lack of clinical observations, absence of an appropriate comparison population (in the case of Whorton et al. 1994), and low confidence in estimates of personal boron exposure preclude these data from providing a basis for deriving an oral MRL.

Animal studies of acute-, intermediate-, and chronic- oral exposure to boric acid or borax consistently identified testicular atrophy and histological lesions and the associated impacts on spermatogenesis as the most sensitive reproductive effect. The majority of studies were performed in rats; however, the effects observed in rats were also observed in mice and dogs. The effects of boron on animal testes appear to be dose- and duration-related.

Acute-duration (2-week) oral gavage or dietary exposures of Wistar rats to 88 mg boron/kg/day as boric acid produced significant damage to male reproductive tissues, but doses of 53 or 44 mg boron/kg/day were without effect (Fukuda et al. 2000; Ku et al. 1993a; Kudo et al. 2000). Exposure to 88 mg boron/kg/day resulted in 12 and 13% reduction in absolute and relative testes weights, respectively, multinucleated giant cell formation, increased residual body-like structures in the testes,

degeneration/necrosis of germ cells, increased cellular debris in the epididymal ducts, exfoliation of round spermatids, and mild inhibition of spermiation (retention of step 19 spermatids at stages IX–XI) (Fukuda et al. 2000; Kudo et al. 2000).

Intermediate-duration gavage studies in rats resulted in similar effects as observed in the acute studies, but at lower exposure levels. Wistar rats given gavage doses of 26 mg boron/kg/day as boric acid for 3 weeks exhibited decreased sperm motility, morphologically-abnormal sperm heads and tails, and increased preimplantation fetal loss when treated males were mated with untreated females; no reproductive effects occurred in this study with exposure to 9 mg boron/kg/day (Yoshizaki et al. 1999). Four-week daily gavage doses of 44 mg boron/kg/day as boric acid resulted in exfoliation of testicular and epididymal germ cells in Wistar rats (Kudo et al. 2000). Fukuda et al. (2000) gave gavage doses of 53 mg boron/kg/day to Wistar rats for 4 weeks and observed 13 and 15% reductions in absolute and relative testes weights, respectively, cellular debris in the testes, caudal and caput epididymis, focal atrophy of the seminiferous tubules, and decreased number of sperm in the ducta lumina. Rats given 4-week daily gavage doses of 88 mg boron/kg/day group exhibited reduced sperm motility, reduced total sperm in caudal epididymis, atrophy of seminiferous tubules, atypical residual bodies, multinucleated giant cell formation, and the inability to impregnate females (Yoshizaki et al. 1999).

Intermediate-duration feeding studies in rats reported effects similar to those of the gavage studies. Rats fed 100 mg boron/kg/day as borax in the diet, but not 50 mg boron/kg/day, for 30 and 60 days showed testicular atrophy (Lee et al. 1978). Sprague-Dawley rats fed 86 mg boron/kg/day as borax in the diet for 30 or 60 days were infertile for 3 or 5 weeks after exposure, respectively (Dixon et al. 1979). Exposure to 43 mg boron/kg/day as borax for 60 days produced reduced testicular and epididymal weights and diameter of seminiferous tubules occurred, and reduced testicular levels of hyaluronidase, sorbitol dehydrogenase, and lactic acid dehydrogenase (isoenzyme-X) at 30 days (Dixon et al. 1979). Mildly inhibited spermiation was observed in Fischer 344 rats exposed to 26 mg boron/kg/day in the diet for 5–9 weeks (Ku et al. 1993a). Fischer 344 rats fed 61 mg boron/kg/day as boric acid for 4 weeks showed inhibited spermiation, appearance of peripheral spermatid nuclei, and spermatocyte sloughing/epithelial disorganization (Treinen and Chapin 1991), while severe inhibition of spermiation and testicular atrophy were observed in Fischer 344 rats exposed to 68 or 52 mg boron/kg/day as boric acid in the diet for 6 or 9 weeks (Ku et al. 1993a). Full recovery from inhibition of spermiation was observed in a 38 mg boron/kg/day group by 16 weeks after cessation of exposure for 9 weeks, but no recovery from testicular atrophy was observed in the 52 and 68 mg boron/kg/day groups up to 32 weeks after exposure ended (Ku et al. 1993a). Dose-related elevations of FSH and LH suggested that boron exposure did not affect the

compensatory response to atrophy (Ku et al. 1993a). In a recent study, Sprague-Dawley rats fed 136 mg boron/kg/day as boric acid for 60 days exhibited decreased weights of testes, epididymes, seminal vesicles, prostate, and vas deferens; decreased sperm motility, spermatocyte, spermatid, and Leydig cell numbers; decreased testosterone levels, sexually aggressive behavior, sexual mounts, number of females impregnated, and viable pups/impregnated female; and increased cellular degeneration, ejaculation time, postejaculatory interval, and fetal resorptions in impregnated females (Nusier and Bataineh 2005).

In intermediate-duration drinking water studies in rats, no reproductive effects (reproductive organ weight or histolopathology) were evident in Sprague-Dawley rats following exposure to 0.6 mg boron/kg/day as borax for 90 days (Dixon et al. 1976). In another study, impaired spermatogenesis was observed in Long-Evans rats given 44.7 mg boron/kg/day as borax in drinking water for 70 days (Seal and Weeth 1980). Complete sterility was observed in Sprague-Dawley rats fed 1,170 ppm boron equivalents in the diet as boric acid or borax (at an estimated dose level of 101 and 116 mg boron /kg/day for males and females); sterility was associated with a lack of viable sperm in atrophied testes in males and decreased ovulation in females (Weir and Fisher 1972). Rats were exposed for 14 weeks before mating in this study. No pregnancies occurred when female rats exposed to this dose level were mated with non-exposed male rats. At lower exposure levels (10 or 30 mg boron/kg/day for males and 12 or 35 mg boron/kg/day for females), no exposure-related adverse effects were found on overall fertility indices in three successive generations (Weir and Fisher 1972).

Studies in mice and dogs support the observations of reproductive effects seen in rats. In a study in which male CD-1 mice were exposed to gavage doses of boric acid of 0, 21, 70, or 210 mg boron/kg/day for 21 days (5 days before mating, during 5 days of mating, and extending to 21 total days of exposure), average testes weights were decreased at doses ≥70 mg boron/kg/day, and exfoliation/disruption of seminiferous tubules and inhibited spermiation were observed at 210 mg boron/kg/day (Harris et al. 1992). Exposed male mice were mated to similarly exposed female mice (except that females were exposed for 8 days before mating), but no exposure-related effects were found on the percentage of females who became pregnant, the number of live pups per litter, or the weight of pups at birth (Harris et al. 1992). Degeneration of the seminiferous tubules was seen in mice exposed to 288 mg boron/kg/day as boric acid in the diet for 13 weeks, while 103-week dietary exposure to 201 mg boron/kg/day as boric acid resulted in testicular atrophy, degeneration of the seminiferous tubules, and interstitial hyperplasia (Dieter 1994; NTP 1987).

In a 2-generation (27-week) feeding study in CD-1 mice using a continuous breeding protocol, seminiferous tubule degeneration, impaired spermatogenesis, and reduced sperm motility resulted from ≥111 mg boron/kg/day as boric acid (Fail et al. 1991). These doses were also associated with reduced litter size and fetal body weight. No effects were observed in a 27 mg boron/kg/day dose group.

In mongrel dogs fed boric acid or borax for 90 days, severe testicular atrophy was seen at 60.5, but not at 6 mg boron/kg/day (Weir and Fisher 1972). With 2 years of exposure, testicular atrophy and spermatogenic arrest were observed in dogs exposed to 22.8, but not in dogs exposed to 6.8 mg boron/kg/day (Weir and Fisher 1972).

Effects of boric acid or borates on female reproductive organs and their functions are less clearly identified and studied in animals than effects on male reproductive organs. When pregnant CD-1 mice were exposed to gavage doses of 210 mg boron/kg/day on gestation days 8–14, all dams failed to deliver litters (Harris et al. 1992). Exposure to 21 or 70 mg boron/kg/day during the same period did not affect littering ability, average litter weight, or the number of live neonates at postnatal days 0, 1, and 4 (Harris et al. 1992). Mechanistic aspects of this effect of gestational exposure on littering capability of pregnant rats are unstudied. As discussed earlier, female Sprague Dawley rats exposed for 14 weeks to 1,170 ppm boron equivalents in the diet as boric acid or borax (estimated dose level of 116 mg boron/kg/day) did not become pregnant when mated with non-exposed males (Weir and Fisher 1972). The female sterility response at this dose level was associated with decreased ovulation.

The highest NOAEL values and all reliable LOAEL values for reproductive effects in animals and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.6 Developmental Effects

No studies were available identifying developmental toxicity in humans from exposure to boron. However, several types of developmental effects (e.g., decreased fetal body weight, increased incidence of skeletal abnormalities) in animals were observed in standard developmental toxicity studies involving oral exposure of pregnant mice, rats, and rabbits to boric acid of borate salts. In addition, reduced pup weight at birth has been observed in animals receiving intermediate-duration exposures.

In mice, reduced fetal body weight and skeletal malformations were seen following acute- and intermediate-duration maternal oral exposures to boric acid.

Pregnant CD-1 mice fed 79 mg boron/kg/day as boric acid on gestation days 0–17 had fetuses with 33% lower body weight compared with controls, while fetal skeletal effects (e.g., short rib XIII, agenesis of lumbar vertabra, fused ribs) were reported at 175.3 mg boron/kg/day on gestation days 0–17 (Heindel et al. 1992, 1994). No effects on fetal development were observed in the 43.4 mg boron/kg/day dose group (Heindel et al. 1992, 1994).

No effects on implantation sites, littering, number of live pups per litter, or postnatal pup weight were observed following gavage exposure of pregnant CD-1 mice to 70 mg boron/kg/day as boric acid on gestation days 8–14 (Harris et al. 1992).

In an acute-duration study, pregnant CD-1 mice were given gavage doses of boric acid on various gestation days to examine the influence of stage of fetal development on skeletal malformations caused by boric acid (Cherrington and Chernoff 2002). When two gavage doses of 70 mg boron/kg as boric acid were given on gestation day 6, 7, 8, 9, or 10, increased incidence of fetuses with cervical rib and rib agenesis were observed in the groups treated on gestation day 8, but not with exposure on gestation days 6, 7, 9, or 10 (Cherrington and Chernoff 2002). Similarly, increased incidences of fetuses with cervical rib, rib agenesis, reduced rib length, and fused ribs were seen after twice daily doses of 70 mg boron/kg on gestation days 6–8. Reduction in length of fetal rib XIII was seen in groups dosed once daily with 88 mg boron/kg/day on gestation days 6–10. A single dose of 131 mg boron/kg on gestation day 8 resulted in increased incidence of fetuses with cervical ossification, while two doses of 131 mg boron/kg on gestation day 8 caused multiple thoracic skeletal malformations. Reduced fetal weight was observed in all treated groups (Cherrington and Chernoff 2002). This study did not identify acute NOAELs for fetal skeletal effects in mice. The study authors suggested that boric acid may alter gastrulation and presomitic mesoderm formation in CD-1 mice, which are key gestational milestones for axial skeletal development.

In rats, acute-duration developmental toxicity data were not available. However, intermediate-duration oral exposure of pregnant rats exhibited effects on fetal skeletal development and fetal weight, similar to those observed in mice. Pregnant Sprague-Dawley rats fed 13.6 boron/kg/day as boric acid in the diet on gestation days 0–20 had reduced fetal body weight, and increased incidence of fetuses with skeletal abnormalities at gestation day 20 occurred in groups of dams fed 28.4 mg boron/kg/day (Heindel et al. 1992). Skeletal abnormalities observed in groups fed 28.4 mg boron/kg/day included agenesis or shortening of rib XIII, increased incidence of fetuses with enlargement of the lateral ventricles of the fetal

brain, and increased resorptions (Heindel et al. 1992). Pregnant Sprague-Dawley rats fed 10 mg boron/kg/day as boric acid on gestation days 0–20 exhibited no developmental effects, but exposures of 13 mg boron/kg/day as boric acid resulted in decreased fetal body weight and skeletal abnormalities seen on gestation day 0. However, in a second phase of this study, identically treated dams were allowed to litter and pups were observed through postnatal day 21. Upon necropsy, these pups did not exhibit significantly different body weights or incidences of skeletal abnormalities seen and fetuses examined on gestation day 0 (Price et al. 1996a, 1998).

Developmental toxicity data in rabbits are available only for acute-duration oral exposures (Price et al. 1996b). Pregnant New Zealand white rabbits given gavage doses of 44 mg boron/kg/day as boric acid on gestation days 6–19 exhibited increased maternal body weight (corrected for gestation) and reduced maternal kidney weight, gravid uterine weight, fetal body weight, number of ovarian corpora lutea, number of implantation sites, and live fetuses, compared with controls. Resorptions and fetal external (cleft palate), visceral (enlarged lateral ventricle of the brain), skeletal (cleft sternum, fused sternebrae), and cardiovascular (enlarged aorta, interventricular septal defect) malformations were increased, compared with controls. No significant maternal or fetal effects were observed following gavage doses of 22 mg boron/kg/day as boric acid. The observed effects are consistent with those seen in acute-, intermediate-, and chronic-duration oral exposures in other animals. These data represent the most sensitive adverse effects observed in any species following acute-duration oral exposures. Thus, an acute-duration MRL of 0.2 mg boron/kg/day was derived based on a NOAEL of 22 mg boron/kg/day and a LOAEL of 44 mg boron/kg/day for developmental effects in New Zealand white rabbits (Price et al. 1996b).

With intermediate-duration oral exposure to boric acid, reduced fetal body weight and skeletal abnormalities were consistently observed in developmental toxicity assays of mice, rats, and rabbits. Skeletal malformations increased in variety and severity with dose. However, reductions in fetal body weight appear to occur at lower exposure levels than those associated with skeletal abnormalities. With intermediate-duration exposure during gestation, the most sensitive developmental effect identified across all three species was reduced fetal weight in pregnant Sprague-Dawley rats fed 13.6 mg boron/kg/day in the diet on gestation days 0–20. This effect was seen at lower intermediate-duration exposure levels than the lowest intermediate-duration oral dose associated with reproductive effects in rats (i.e., a LOAEL of 26 mg boron/kg/day was identified for inhibition of spermiation in rats) (Ku et al. 1993a). An intermediate oral MRL of 0.2 mg boron/kg/day was calculated as described in the footnote on Table 3-2,

based on a benchmark dose analysis (Allen et al. 1996) of combined data sets (Heindel et al. 1992; Price et al. 1996a) for reduced fetal body weight in rats.

The highest NOAEL values and all reliable LOAEL values for developmental effects in animals and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.7 Cancer

Three epidemiological studies have associated increased boron intake in drinking water with decreased incidences of prostate and vaginal cancer. Cui et al. (2004) used the cross-sectional data from the NHANES III study, conducted from 1988 to 1994, which contained health and diet information for the non-institutionalized U.S. population. These investigators reported that men with mean intakes of ≥1.54 mg boron/day had significantly less risk of developing prostate cancer than men ingesting ≤0.52 mg/day. This study was limited by its cross-sectional design and reliance on 1-day recall of diet information to estimate boron exposure. A second study (Barranco et al. 2007) on a Texas population correlated increased boron in groundwater with reduced prostate cancer incidence rates. However, the observed correlation appeared to be driven primarily by 2–3 specific cases. Korkmaz et al. (2007) studied 1,059 rural Turkish women and associated higher boron intake (as evidenced by approximately 8-fold higher urinary boron concentration) with lower incidences of cervical cytopathology (0 findings in the high-boron group, 15 cases in the low-boron group). While this study did attempt to correct for lifestyle factors and other genotoxic confounders, it was cross-sectional in design. The hypotheses drawn from these studies are interesting; however, no clinical studies in humans or animals are available to substantiate effects of anti-tumor protection offered by boron.

No evidence of exposure-related cancer was observed in rats exposed to 81 mg boron/kg/day as boric acid or borax for 2 years (Weir and Fisher 1972), dogs exposed to 6.8 mg boron/kg/day as boric acid or borax for 2 years (Weir and Fisher 1972), or mice exposed to 201 mg boron/kg/day as boric acid for 2 years (Dieter 1994; NTP 1987). In nude mice subcutaneously injected with human LNCaP cells (prostate tumor clones), oral gavage doses of boric acid were given for 8 weeks (Gallardo-Williams et al. 2004) to determine if boron offered protection against prostate tumor growth. Although there was no significant difference between control and boron-treated mice in tumor incidences, the tumor sizes in mice given 1.7 mg boron/kg/day were significantly smaller and the serum level of tumor specific antigen (PSA) was significantly less than controls.

3.2.3 Dermal Exposure

Information on dermal toxicity in humans involves exposure to the borates (as boric acid or borax), while the animal data involves exposure to boron oxide, which easily converts to boric acid in humid air or upon entering the mucosal layer of tissues.

3.2.3.1 Death

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

3.2.3.2 Systemic Effects

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

Hematological Effects. Draize and Kelley (1959) reported the application of 25–200 mg/kg/day boric acid in aqueous solution did not produce hematological changes when rubbed onto intact skin during a 90-day rabbit study. No quantitative data were provided; therefore, these results could not be evaluated.

Dermal Effects. Human data are limited to case reports of accidental exposure of the head. Three male workers (59-year-old waste handler and 34- and 36-year-old automotive mechanics) presented with general or focal alopecia of the scalp, presumably from spillage or wiping of boric acid or borax, respectively, onto the head (Beckett et al. 2001). In the case of the waste handler, the concentration of boric acid in the milieu of other known solvents in the waste tank was unknown. In the cases of the automotive workers, exposure was determined to arise from under-the-chassis flushing of automobile radiators which contained coolant solutions of ethylene glycol and 1–5% borax. Actual exposures could not be determined. Blood sample analysis revealed no elevated blood boron levels in any of the subjects. Gradual and full hair re-growth occurred.

In animals, application of 1 g boron oxide dust to a 25 cm^2 area of the skin of four rabbits produced erythema that lasted for 2–3 days (Wilding et al. 1959).

Ocular Effects. Instillation of boron oxide dust (50 mg) into the eyes of four rabbits produced conjunctivitis (Wilding et al. 1959).

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

3.2.3.3 Immunological and Lymphoreticular Effects

3.2.3.4 Neurological Effects

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

3.2.4 Other Routes of Exposure

Direct application of a solution containing 6.3 mg boron (as sodium perborate monohydrate) onto the cornea of rabbits resulted in mild irritancy of the epithelium and superficial stroma (Maurer et al. 2001).

3.3 GENOTOXICITY

No studies were located regarding genotoxic effects of boron by inhalation, oral, or dermal exposure in humans.

Results were predominantly negative in bacterial assays and in *in vitro* (Table 3-3) mammalian assays, including tests for chromosomal aberrations, gene mutation (Benson et al. 1984; Demerec et al. 1951; Haworth et al. 1983; Landolph 1985; NTP 1987), and cell transformation (Landolph 1985). Induction of β-galactosidase as part of the SOS response was observed in *Escherichia coli* PQ37, both with and without S-9 metabolic activation (Odunola 1997). In pregnant rats given two gavage doses of 88 mg/boron/kg/day (as boric acid) on gestation day 9, a cranial shift in the anterior limits of the *hoxa6* and *hoxc6* genes was detected in the fetuses (Wery et al. 2003). These genes have been associated with control of position and development of the fetal vertebrae. The response of the *hoxa6* and *hoxc6* genes to *in utero* exposure to high doses of boron (as boric acid) may be associated with abnormalities of the rodent vertebrae. Thus, genotoxicity may be an area of concern following exposure

Table 3-3. Genotoxicity of Boron *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Prokaryotic organisms:				
Salmonella typhimurium	Gene mutation	–	–	Haworth et al. 1983
	Gene mutation	–	–	Benson et al. 1984
	Gene mutation	–	–	NTP 1987
Escherichia coli	Gene mutation	–	–	Demerec et al. 1951
Mammalian cells:				
Mouse lymphoma	Gene mutation	–	–	NTP 1987
Mouse embryo fibroblast	Gene mutation	NA	–	Landolph 1985
Human foreskin fibroblast	Gene mutation	NA	–	Landolph 1985
Chinese hamster ovary	Gene mutation	NA	–	Landolph 1985
Chinese hamster ovary	Chromosomal aberration	–	–	NTP 1987

— = negative result; NA = not applicable

to boron in humans if the *hox* gene functionality is conserved across species and if the human *hox* gene is sufficiently responsive *in utero* following boron exposure.

3.4 TOXICOKINETICS

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

Reports of upper respiratory tract symptoms of irritation following exposure to boron oxide and boric acid dusts suggest that boron can deposit in the upper airway (Garabrant et al. 1984, 1985). Borax production workers were found to have approximately an order of magnitude higher blood and urine concentrations of boron at the end of a work shift compared to the beginning, suggesting that inhaled boron is absorbed and systemically distributed (Culver et al. 1994a).

3.4.1.2 Oral Exposure

Near-complete gastrointestinal absorption was indicated in humans as evidenced by the urinary recovery of 93.9% of the ingested dose of boric acid over a 96-hour collection period (Jansen et al. 1984a). Dourson et al. (1998) reviewed data from the literature to estimate oral absorption fractions of 81–92% for humans and 95% for animals (rats).

3.4.1.3 Dermal Exposure

No quantitative studies were located regarding boron absorption in humans or animals after dermal exposure. Urinary excretion studies in humans (Section 3.4.4.3) suggest there is very little absorption of boron through intact skin. Excretion studies (Section 3.4.4.3) in rabbits suggest that boron is readily absorbed following contact with damaged skin (Draize and Kelley 1959).

3.4.2 Distribution

No quantitative studies were located regarding distribution in humans.

3.4.2.1 Inhalation Exposure

No studies were located regarding distribution of boron in animals after inhalation exposure.

3.4.2.2 Oral Exposure

Boron evenly distributed to liver, kidney, brain, muscle, adrenals, epididymis, testes, seminal vesicles, and blood, but not fat, of male rats fed 61 mg boron/kg/day as boric acid (9,000 ppm) for 1–28 days (Ku et al. 1991; Moseman 1994 ; Treinen and Chapin 1991), reaching steady-state by 4 days. Blood and testes boron levels were similar in rats fed 26–68 mg boron/kg/day as boric acid (3,000–9,000) for 9 weeks (Ku et al. 1991). However, boron accumulated in bone in male rats fed 61 mg boron/kg/day (as boric acid) for 9 weeks, with achievement of steady-state at 4 weeks. Bone levels were approximately 3-fold higher than soft tissue levels (Moseman 1994).

3.4.2.3 Dermal Exposure

No studies were located regarding distribution of boron in animals after dermal exposure.

3.4.3 Metabolism

As an inorganic chemical, boron is not expected to be metabolized by humans or animals. Studies of inhalation and oral exposure of animals and humans to borates have consistently reported recovery of the parent borate only in the blood, tissues, and urine (Culver et al. 1994a; Draize and Kelley 1959; Jansen et al. 1984a; Ku et al. 1991; Moseman 1994; Treinen and Chapin 1991).

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

No studies were located regarding excretion in humans after inhalation exposure to boron. In rats that inhaled average concentrations of 77 mg/m^3 boron oxide aerosols over a 22-week period, an average of 11.90 mg boron/kg/day was detected in the urine compared to 0.24 mg/kg/day in untreated control groups (Wilding et al. 1959).

3.4.4.2 Oral Exposure

Over 93% of the administered dose was excreted in the urine of six male volunteers 96 hours after administration of a single oral dose of 1.9 mg boron/kg (as boric acid) (Jansen et al. 1984a). An analysis of nine cases involving boric acid poisoning revealed a mean half-life of 13.4 hours (range 4–27.8 hours).

There was no correlation between half-life and calculated serum boric acid level at t_o (r=0.08, p=0.84) (Litovitz et al. 1988). Boric acid was detected in urine of patients 23 days after a single ingestion (Wong et al. 1964). Renal clearance of dietary boron from fifteen pregnant women was calculated to be 1.02 mL/minute/kg, or 66.1 mL/minute (Pahl et al. 2001).

In rabbits, 50–66% of the administered dose was recovered in urine after ingestion of 17.1–119.9 mg boron/kg/day as boric acid (Draize and Kelley 1959). In rats fed 26–68 mg boron/kg/day as boric acid (3,000–6,000 ppm) for 9 weeks, boron concentrations in bone began decreasing after cessation of exposure; however, bone levels remained approximately 3-fold higher than controls for up to 32 weeks (Chapin et al. 1997; Moseman 1994). Blood levels in these same animals returned to control levels within 7 days of exposure cessation (Ku et al. 1991). Using literature data, Dourson et al. (1998) estimated the fraction eliminated of absorbed boron to be 67–98% in humans and 99% in rats. These investigators also calculated clearance values of 40 mg/kg/hour in humans, 163 mg/kg/hour in rats, and 397 mg/kg/hour in pregnant rats. Pregnancy did not affect renal clearance (0.2 L/hour/kg or 1.0 mL/minute) or elimination half-life (3.2 hours) in rats given gavage doses of 0.05–5 mg boron/kg/day (as boric acid) on gestation day 16 (Vaziri et al. 2001).

3.4.4.3 Dermal Exposure

Limited data in humans suggest that very little absorption of boron occurs through intact skin. There was no increase in the urinary excretion of boron in one human subject following the application of 15 g boric acid (37.5 mg boron/kg body weight) on the forearm for 4 hours (Draize and Kelley 1959).

Animal studies support human findings. Draize and Kelley (1959) applied 200 mg/kg as boric acid to intact, abraded or burnt, and partially denuded skin of rabbits. Net urinary excretion of boric acid per 24 hours during 4 consecutive days of compound treatment was 1.4, 7.6, and 21.4 mg/kg, respectively (0.25, 1.3, and 3.7 mg boron/kg, respectively).

3.4.4.4 Other Routes of Exposure

In eight adult volunteers administered a single dose of boric acid (562–611 mg) by intravenous infusion, 98.7% of the administered dose was recovered in urine 120 hours after injection (Jansen et al. 1984b). Renal blood clearance averaged 39.1 mL/minute per 1.73 m^2 surface area in eight adult human subjects administered intravenous injections of 35 mg boron/kg (as sodium pentaborate). Urine boron concentrations on the day of administration averaged 1.19 mg/mL (Farr and Konikowski 1963). In rats

administered an intravenous infusion of 86 mg boron/kg (as borax) (Tagawa et al. 2000), boron distributed rapidly to the extravascular tissues, giving a steady state volume of distribution of 1.19 L/kg. Excretion of boron was rapid, with 87.6% eliminated in the urine by 2 hours after infusion. Pharmacokinetic analysis of the blood time course data resulted in an estimated elimination rate constant (K_{el}) of 0.15 $hour^{-1}$ and a clearance rate of 0.11 L/hour/kg. The elimination half-life was 8.43 hours.

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

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

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

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

provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

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

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

If PBPK models for boron 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.

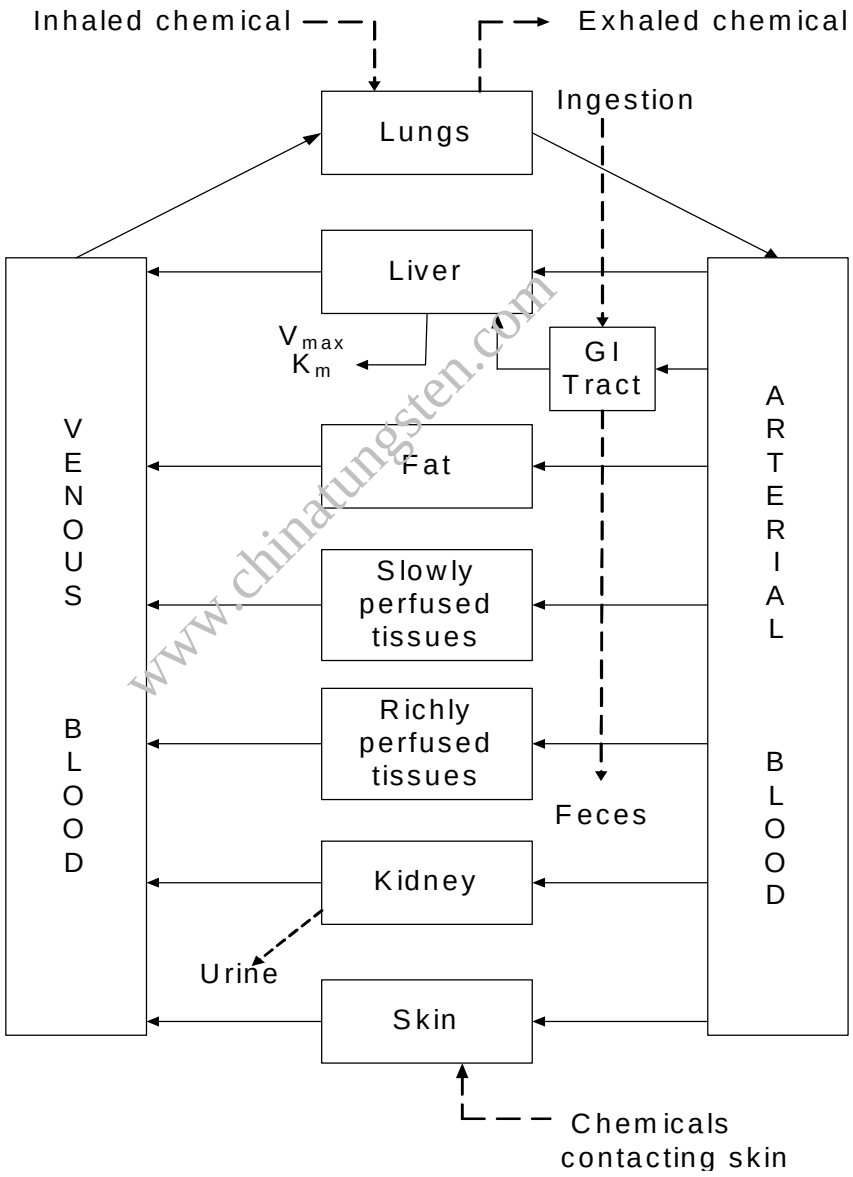
There are no PBPK models available for boron.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Absorption. Boron is absorbed across pulmonary tissues into the blood, as seen in workers exposed to borate dusts, who were found to have higher blood and urine boron concentrations at the end of a work shift compared to the beginning of the shift (Culver et al. 1994a). Boron is almost completely absorbed in the gastrointestinal tract, with up to 92 and 95% of ingested dose being recovered in the urine (Dourson et al. 1998). No data are available to indicate whether boron is actively transported or passively diffused across pulmonary or gastrointestinal tissues. Diet may influence the rate of boron absorption in the gut, as higher initial boron levels were found in the urine of humans given boron in an ointment vehicle, compared to administration via a water vehicle (Schou et al. 1984). Boron was not found to be absorbed across intact human or animal skin (Draize and Kelley 1959)

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



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

Source: adapted from Krishnan and Andersen 1994

Distribution. Boron is distributed readily to all body tissues. Tissue levels from daily doses were observed to achieve steady-state with plasma in all tissues examined, including neurological and reproductive tissues, with the exception of bone and adipose tissues (Ku et al. 1991. Bone serves as a storage depot for boron, while adipose tissue has a lower affinity for boron than other soft tissues. The mechanism(s) of transport across tissue membranes and into bone are not known. No data were available identifying binding of boron to a carrier protein in the blood or plasma membranes.

Metabolism. Boron is a trace element and is not metabolized in the body. Borates exist in the body as boric acid, the only form of boron recovered in the urine.

Excretion. Excretion of systemically absorbed born is accomplished primarily through renal elimination, with minor fractions excreted in the saliva, sweat, and feces (Jansen et al. 1984a). No data are available regarding the contribution of tubular absorption of boron in the kidney. Glomerular filtration rate is likely the dominant factor in renal elimination of boron. As such, the systemic elimination of boron may be compromised in populations with reduced glomerular filtration rates (Dourson et al. 1998), such as preeclamptic women. This assumption is used in deriving chemical-specific uncertainty factors, which themselves are used for deriving the intermediate-duration oral MRL (Appendix A).

3.5.2 Mechanisms of Toxicity

No studies were available in humans describing a mechanism of toxicity for neurological, gastrointestinal, hepatic, or renal effects observed in case reports of high-dose poisoning incidents. In animals, reproductive and developmental effects have been the most sensitive toxic end points observed.

Although several studies have examined possible mechanisms for reproductive toxicity, the actual toxic mechanism remains unknown. In rats, delayed spermiation (inhibited release of mature sperm) appears to be the hallmark event in testicular toxicity, followed by exfoliation of germ epithelium and atrophy at higher doses (Treinen and Chapin 1991). Leydig and Sertoli cell cultures exposed to 10 mM boric acid did not exhibit reduced responsiveness to induction of testosterone production, but exhibited reduced intracellular cAMP levels following FSH stimulation (Ku et al. 1993b). Further, lactate and pyruvate (the primary energy sources for Sertoli cells) production (possibly from boronation of NAD cofactors [Ku et al. 1993b]) and deoxyribonucleic acid (DNA) synthesis were significantly reduced, suggesting that germ epithelial sloughing and testicular atrophy may result from impaired energy production and mitosis/meiosis in the Sertoli cells

(Fail et al. 1998). However, *in vivo* delayed spermiation appears to occur at lower Sertoli cell exposure levels than disruption of energy production and DNA synthesis, making it difficult to conclude whether reproductive effects are hormonally or metabolically-mediated (Fail et al. 1998; Ku et al. 1993a).

The mechanism of toxicity for developmental effects is also unknown. Fail et al. (1998) suggest that the reduction in fetal body weight (the most sensitive end point observed in rats [Heindel et al. 1992]) may be due to mitotic inhibition observed in viruses, bacteria, insects, yeasts, and animals. Hyperacetylation of embryonic mouse tissues is highly associated with skeletal malformations following exposure to histone deacetylase inhibitors such as valproic acid and trichostatin A. Mice given intraperitoneal doses of 175 mg boron/kg (as boric acid) on gestation day 8 exhibited hyperacetylation of embryonic somites, inhibition of histone deacetylase, and increased incidences of skeletal malformations (fused ribs and vertebra, changes in the typical number of axial segments in different axial districts). The association of these biochemical and morphological effects suggest that boric acid-induced skeletal malformations may result from inhibition of histone deacetylase. Wery et al. (2003) reported a cranial shift in the anterior limits of the *hoxa6* and *hoxc6* genes in the fetuses of pregnant rats given two gavage doses of 88 mg/boron/kg/day (as boric acid) on gestation day 9. The control of position and development of the fetal vertebrae have been associated with the activity of these genes (see Section 3.3). It is not known whether inhibition of histone deacetylase, as suggested by Fail et al. (1998) is involved with the response of the *hoxa6* and *hoxc6* genes to *in utero* exposure to high doses of boron.

3.5.3 Animal-to-Human Extrapolations

Similarities in rodents and humans for boron toxicokinetics and reproductive physiology suggest that the animal toxicity data are relevant for human risk assessment. Animal and rodents studies indicate that boron is readily absorbed (particularly via the oral route), not metabolized, and extensively eliminated via urinary excretion (Section 3.4). Male humans and rodents share similar physiological structures and hormonal control mechanisms of the reproductive system, suggesting a similar target of toxicity for reproductive effects. Similarly, the sequence of fetal developmental steps is similar between the species. Lack of human data, particularly reproductive and developmental data, for effects observed in animal studies introduce uncertainty into the extrapolation of animals data to humans.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals

with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Thomas and Colborn (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No studies were located regarding endocrine disruption in humans after exposure to boron. While depressed testosterone blood levels was observed in rats fed diets with 61 mg boron/kg/day as boric acid (Treinen and Chapin 1991), GnRH challenge in boron-fed rats (Fail et al. 1998) resulted in LH responses similar to controls and an exacerbated FSH response relative to controls, suggesting that peripheral hormonal changes were not due to neuroendocrine toxicity, but possibly to Leydig and Sertoli cell-specific effects (Fail et al. 1998).

No *in vitro* studies were located regarding endocrine disruption of boron.

3.7 CHILDREN'S SUSCEPTIBILITY

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

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

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life, and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are proportionately larger than adults (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed

efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

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

Human data of boron toxicity in children and humans due to high-dose exposures are not adequate to identify the presence or lack of children's susceptibility. Normal boron blood levels in children and infants range from 0 to 1.25 µg/mL (Fisher and Freimuth 1958; O'Sullivan and Taylor 1983). Infants exhibiting adverse effects after ingestion of boric acid in infant formula had boron blood levels (reported as borate) of 20–150 µg/mL, with fatal cases having blood levels of 200–1,600 µg/mL (Wong et al. 1964). Comparatively, adult serum boron level (as boric acid) of 2,320 µg/mL was not associated with significant toxicity (Linden et al. 1986).

No animal studies were located regarding susceptibility of immature animals to boron toxicity. However, oral exposure studies in pregnant animals have identified developmental effects in fetus exposed to boron (as borax or boric acid) *in utero*. No developmental effects were observed in animals following inhalation exposures. The observed effects from oral exposure include skeletal malformations and cardiovascular abnormalities. The most sensitive effect identified was reduced fetal body weight, which consistently occurred in animals at lower doses than required for skeletal malformations or other effects. The acute- and intermediate-duration oral MRLs are based on reduced fetal body weight in rats and should be protective of children developing in the womb.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

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

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to boron are discussed in Section 3.8.1.

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

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

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Boron

Boron in blood and urine can be used as an indicator of exposure to boron. Normal dietary concentrations of boron in the blood of humans range from 0 to 1.25 µg/mL in children and infants (Fisher and Freimuth

1958; O'Sullivan and Taylor 1983). Boron blood levels (reported as borate) of 20–150 µg/mL have been associated with adverse systemic effects in infants who ingested boric acid in infant formula (Wong et al. 1964). Boron concentrations, expressed as borate, reported in fatal cases vary from 200 to 1,600 µg/mL in infants (Wong et al. 1964). In adults, a serum boron level (as boric acid) of 2,320 µg/mL was not associated with significant toxicity (Linden et al. 1986).

Urinary excretion levels can also be useful indicators of elevated total body burden of boron. Concentrations of boron in the normal population range from 0.07 to 0.15 mg/100 mL (Vignec and Ellis 1954) and from 0.004 to 0.66 mg/100 mL (Imbus et al. 1963). In one infant, the urine contained 13.9 mg boron/liter as borax or 1.38 mg boron/mL of boric acid following ingestion of a borax and honey mixture over a period of 12 weeks (Gordon et al. 1973). Virtually complete urinary excretion was indicated by the recovery of 93.9% (over a 96-hour collection period) of a boric acid solution ingested by three volunteers (Jansen et al. 1984a).

Neurological, dermal, gastrointestinal, liver, and kidney effects in humans have been associated with exposure to boron. Studies in animals have demonstrated gonadal injury. Various clinical and biochemical tests exist that may provide useful information on exposure. However, similar effects are caused by a variety of other substances and are, therefore, not specific for boron exposure.

3.8.2 Biomarkers Used to Characterize Effects Caused by Boron

Central nervous system injury, gastrointestinal effects, and skin damage are characteristic manifestations of boron toxicity in humans. Liver and kidneys in humans and testes in animals can also be affected. Various clinical and biochemical changes associated with these effects may be measured to detect the extent of exposure to boron. There is no single biological indicator of boron exposure; consequently, several parameters must be measured including boron levels in urine and blood and biochemical changes for systemic and neurological effects.

Neurological damage has been reported in humans. Neurological effects reported in humans have focused primarily on histopathological alterations. No data were provided on biochemical changes. In animals, testicular atrophy and reduced sperm production have been demonstrated following chronic boron exposure. There are clinical and biochemical tests to detect neurological and gonadal injury, but these are not specific for boron exposure. Sparse data in animals suggest some biochemical changes; for instance, cerebral succinate dehydrogenase was increased in rats after boron exposure. Animal data

further demonstrate biochemical alterations following gonadal injury. Dose-dependent reduction in hyaluronidase, sorbitol dehydrogenase, and lactic acid dehydrogenase (isoenzyme-X) were observed in rats following boron exposure.

3.9 INTERACTIONS WITH OTHER CHEMICALS

No studies were located regarding the influence of other chemicals on the toxicity of boron.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to boron than will most persons exposed to the same level of boron 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 boron, or compromised function of organs affected by boron. Populations who are at greater risk due to their unusually high exposure to boron are discussed in Section 6.7, Populations with Potentially High Exposures.

No data were located identifying a population that is unusually susceptible to boron toxicity. Case reports in humans suggest that large variability exists with the human population to the lethal effect of boron. However, there are no data to suggest which segment of the population is more susceptible to boron.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

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

Ellenhorn MJ, Schonwald S, Ordog G, et al., eds. 1997. Ellenhorn's medical toxicology. Diagnosis and treatment of human poisoning. 2nd ed. Baltimore, MA: Williams & Wilkins, 1098-1100, 160t, 162t.

Goldfrank LR, Flomenbaum NE, Lewin NA, et al., eds. 2002. Goldfrank's toxicologic emergencies. 7th ed. New York, NY: McGraw-Hill, 1282, 1289-1290, 1134.

Viccellio P, Bania T, Brent J, et al., eds. 1998. Emergency toxicology. 2nd ed. Philadelphia, PA: Lippincott-Raven, 448-449, 470, 1141.

Human exposure to boron may occur by inhalation, ingestion, or dermal contact (see Chapter 6). Boron in the form of boric acid or borate dust is an upper respiratory tract irritant following inhalation and may also irritate the eyes and skin. Ingestion of boron may cause gastrointestinal, neurological, hepatic, renal, and dermal effects (see Section 3.2). General recommendations for reducing absorption of boron following exposure have included removing the exposed individual from the contaminated area and removing the contaminated clothing. If the eyes and skin were exposed, then they should be flushed with water.

3.11.1 Reducing Peak Absorption Following Exposure

Nausea, vomiting, and diarrhea have been induced by ingestion of boron in humans. Some authors recommend reducing absorption of boron from the gastrointestinal tract by administration of emetics (e.g., syrup of ipecac) and cathartics (e.g., magnesium sulfate) (Stewart and McHugh 1990). Caution should be taken, however, not to induce further damage to the esophageal mucosa or to cause aspiration of the vomit into the lungs during emesis. There is disagreement regarding the efficiency of activated charcoal in preventing absorption of boron from the gastrointestinal tract following oral exposure (Ellenhorn and Barceloux 1988; Stewart and McHugh 1990). It has been suggested that activated charcoal be administered following gastric evacuation, but its effectiveness has not been established (Ellenhorn and Barceloux 1988). Administration of intravenous fluids may be required if severe dehydration or shock develop and local skin care may be necessary if skin desquamation occurs (Stewart and McHugh 1990). In addition, the treatment of boron poisoning may require a control for convulsions.

3.11.2 Reducing Body Burden

Elemental boron is not metabolized (see Section 3.4). Studies in volunteers indicated that most of the administered dose is excreted in the urine within few days (Jansen et al. 1984a). Saline diuresis has been suggested to enhance urinary excretion of boron (Goldfrank et al. 1990). Exchange transfusions, peritoneal dialysis, or hemodialysis may be employed to lower plasma boron levels following either acute or chronic intoxication. There are indications that hemodialysis is the most effective of these procedures (Goldfrank et al. 1990; Naderi and Palmer 2006; Stewart and McHugh 1990).

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

No studies were available to support measures to interfere with the mechanism of action for boron once it has been absorbed.

3.12 ADEQUACY OF THE DATABASE

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

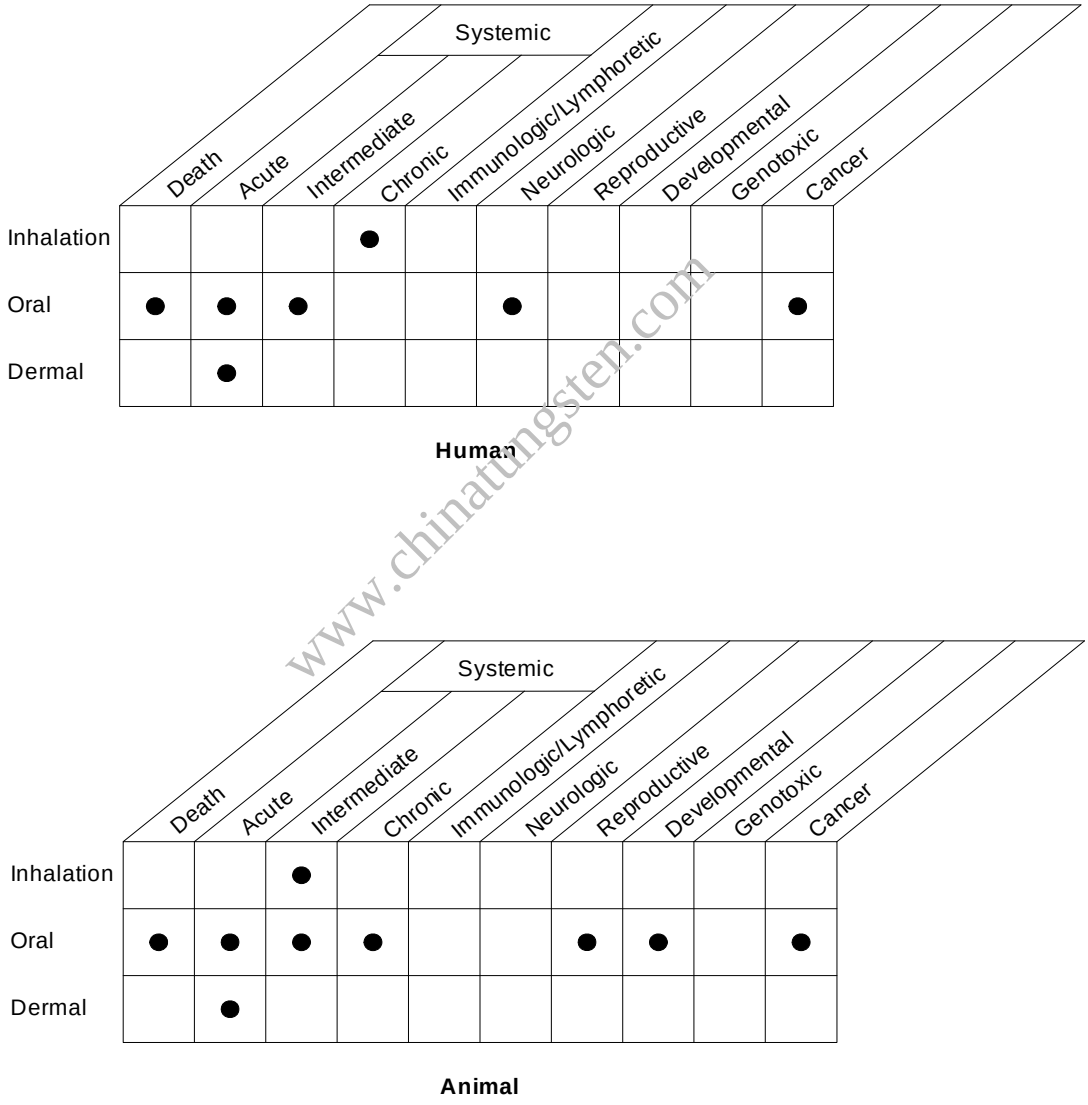
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean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

3.12.1 Existing Information on Health Effects of Boron

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to boron are summarized in Figure 3-4. The purpose of this figure is to illustrate the existing information concerning the health effects of boron. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Most of the information concerning health effects of oral exposure to boron in humans is found in case reports of accidental acute and intermediate ingestion of boron. Controlled-exposure studies of volunteers

Figure 3-4. Existing Information on Health Effects of Boron



and cross-sectional surveys of borate mining and production workers have identified acute upper respiratory and ocular irritation as an effect of concern from acute inhalation exposure. Epidemiology studies of intermediate- to chronic-duration exposures (involving repeated occupational exposure to dusts of borates or repeated exposure to boron in drinking water) have not clearly identified a toxic effect in humans, but have found no associations between boron exposure and impaired pulmonary function or impaired fertility. Information on acute dermal exposure exists, but none was found on effects after intermediate- and chronic-duration exposure.

In animals, information exists on health effects following acute, intermediate, and chronic oral exposure to boric acid or borax. Comprehensive acute toxicity studies involving inhalation exposure to boron compounds are not available, with the exception of a study of mice exposed by inhalation to diborane gas for 2 or 4 weeks. Diborane gas is expected to have a very short half-life in the environment because of its reactivity. Thus, it is not expected to be a significant environmental toxicant, except in workplaces where it might be used and accidentally released. Health effects have been examined in rats and dogs exposed by inhalation to boric oxide aerosols for intermediate durations. Studies of health effects in animals exposed by inhalation to boron compounds for chronic durations are not available. Health effects have been observed in animals following acute dermal exposure, but no toxicity studies of animals dermally exposed for intermediate and chronic durations are available.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. Associations between acute inhalation exposure to borate dusts and increased prevalence of self-reported symptoms of irritation of the upper respiratory tract and eyes in workers under workplace conditions (Garabrant et al. 1984, 1985; Hu et al. 1992; Wegman et al. 1994) and in volunteers under controlled exposure conditions (Cain et al. 2004) form the basis of an acute-duration inhalation MRL. Supporting data on dose-response relationships for mild respiratory and ocular irritation from studies of animals exposed by inhalation for acute durations are not available.

Case reports of acute oral poisonings with boric acid do not clearly identify toxicity targets and dose-response relationships in humans, but reported effects in fatal cases include degenerative changes in the liver, kidney, and brain (Chao et al. 1991a, 1991b; Wong et al. 1964). In animal studies, acute-duration oral exposure to boric acid or borates has been associated with effects on the male reproductive organs (e.g., decreased testicular weight and altered sperm morphology) in Wistar rats exposed to gavage boric acid doses of 88 mg boron/kg/day for 2 weeks (Fukuda et al. 2000; Kudo et al. 2000) and

developmentally toxic effects (including reduced fetal weight and increased skeletal variations or malformations) in CD-1 mice exposed during gestation to boric acid doses as low as 70 mg boron/kg (2 times/day) (Cherrington and Chernoff 2002) and in New Zealand rabbits exposed during gestation (days 6–19) to doses of 44 mg boron/kg/day (Price et al. 1996b). A NOAEL of 22 mg boron/kg/day for developmental effects in rabbits (Price et al. 1996b) serves as the basis of the acute-duration oral MRL for boron.

Dermal/ocular effects have been associated with dermal exposure in humans (Beckett et al. 2001) and animals (Wilding et al. 1959). The irritation effects observed in animals may have been due to the exothermic rehydration reaction of the anhydride boron oxide.

No further acute-duration health effect studies are recommended at this time.

Intermediate-Duration Exposure. No studies are available that establish associations between intermediate-duration oral exposures to boron compounds and health effects in humans. Case reports of intermediate-duration exposure to humans are limited to reports on infants exhibiting neurological effects after ingestion of high levels of boron as boric acid. Seizure disorders occurred during oral exposures of infants to borax lasting 4–12 weeks, with cumulative approximate doses of 12–120 g (Gordon et al. 1973; O'Sullivan and Taylor 1983). No associations were found between elevated levels of borates in drinking water and fertility rates in surveys of Turkish subpopulations expected to have intermediate- to chronic-duration exposures to boron (Sayli 1998a, 1998b, 2003; Sayli et al. 1998). Likewise, cross-sectional surveys of boron mining and processing workers in California (Whorton et al. 1994) and China (Chang et al. 2006) failed to find associations between boron exposure (which may have included oral exposure to boron) and adverse effects on indices of fertility.

Studies in animals indicate that reproductive and developmental effects are the most sensitive effects associated with intermediate-duration oral exposures to boric acid or borates. Testicular atrophy and histopathology, sperm abnormalities, and reduced sperm production have been observed in mice, rats and dogs after intermediate-duration ingestion of doses ≥26 mg boron/kg/day as boric acid (Dieter 1994; Dixon et al. 1976, 1979; Fail et al. 1991; Fukuda et al. 2000; Harris et al. 1992; Ku et al. 1993a; Kudo et al. 2000; Lee et al. 1978; NTP 1987; Nusier and Bataineh 2005; Seal and Weeth 1980; Weir and Fisher 1972; Yoshizaki et al. 1999). Complete sterility was observed in Sprague-Dawley rats fed boric acid or borax in the diet (101 and 116 mg boron/kg/day for males and females, respectively) for 14 weeks before mating; sterility was associated with a lack of viable sperm in atrophied testes in males and decreased

ovulation in females (Weir and Fisher 1972). No pregnancies occurred, when female rats exposed to this dose level were mated with non-exposed male rats. At lower exposure levels (10 or 30 mg boron/kg/day for males and 12 or 35 mg boron/kg/day for females), no exposure-related adverse effects were found on overall fertility indices in three successive generations (Weir and Fisher 1972). Developmental effects (including decreased fetal weight, increased incidence of skeletal variations and malformations, and increased resorptions) have been observed in offspring of rat and mouse dams exposed to 13–79 mg boron/kg/day as boric acid during gestation (Heindel et al. 1992, 1994; Price et al. 1996a). Multiple developmental end point data from the rat studies by Heindel et al. (1992) and Price et al. (1996a) were pooled and subjected to benchmark dose analyses (Allen et al. 1996) to derive a benchmark-dose point of departure of 10.3 mg boron/kg/day for the intermediate-duration oral MRL for boron.

Additional cross-sectional or prospective surveys of reproductive health end points in populations exposed to elevated levels of boron compounds in drinking water may help to better identify reproductive toxicity and developmental toxicity as potential health effects in humans with elevated oral exposure to boron for intermediate or chronic durations.

Increased frequencies of symptoms of acute upper respiratory and ocular irritation have been reported in workers exposed repeatedly by inhalation to boron oxide and borate dusts at average concentrations of 1.8 and 3.1 mg boron/m^3, and employed in the borax industry for a mean duration of 11.4 years (SD 8.1 years), compared with a reference population (Garabrant et al. 1984, 1985); however, it is uncertain if these acute symptoms were due to acute or repeated exposure. Later studies of a different design indicated that acute irritation symptoms in these workers are due to acute exposures, and that pulmonary function variables (e.g., FEV_1) were not significantly influenced by exposure over a 7-year period of employment (Hu et al. 1992; Wegman et al. 1994). These results are adequate to form the basis of an acute inhalation MRL for boron, but do not clearly indicate whether the dose-response relationships for acute boron-induced upper respiratory and ocular irritation symptoms are changed with intermediate or chronic durations of exposure. Because exposure-related effects on pulmonary function variables were not evident during a 7-year period between the studies of Garabrant et al. (1984, 1985) and Wegman et al. (1994), the results provide some confidence that the acute-duration inhalation MRL may by protective for intermediate- and chronic-duration exposures.

Intermediate-duration inhalation exposure studies in animals are restricted to a series of studies in which albino rats were exposed to boric oxide aerosols for 6 hours/day, 5 days/week for 10 weeks at an average concentration of 73 mg boron/m^3 (n=20 rats), 12 weeks at 27 mg boron/m^3 (n=4), or 24 weeks at 12 mg

boron/m^3 (n=70) (Wilding et al. 1959). Histopathologic examination of a comprehensive set of tissues (lung, trachea, pancreas, thyroid, adrenal, eye, femur, rib, bone marrow, liver, heart, spleen, kidney, brain, stomach, intestine, ovary, testis, lymph node, and muscle) in exposed and control rats revealed no exposure-related lesions, with the exception that some rats exposed to the highest concentration (73 mg boron/m^3) showed a reddish nasal exudate. Although dogs were included in this study (three dogs were exposed to 9 mg boron/m^3 for 23 weeks), end points were restricted to clinical signs of toxicity, body weight, hematological end points, and sulfobromophthalein retention, a measure of liver function (Wilding et al. 1959). No exposure-related effects on these end points were found in exposed dogs, compared with controls. Because the NOAELs identified in the rat and dog studies were higher than concentrations associated with acute respiratory and ocular irritation in humans acutely exposed to boron (Cain et al. 2004; Wegman et al. 1994), the intermediate-duration inhalation database was considered inadequate for derivation of an MRL.

Additional prospective health evaluations of respiratory function and reproductive and developmental variables in borate mining and processing workers with intermediate- and chronic-duration exposures may help to better identify impaired respiratory function, impaired reproductive performance, and developmental effects as critical effects in humans from intermediate- or chronic duration exposure to boron compounds.

Chronic-Duration Exposure and Cancer. No studies are available that establish associations between chronic-duration oral exposures to boron compounds and noncancer or cancer effects in humans. As discussed in the previous section, no associations were found between exposure to borates or boric oxide and indices of fertility in surveys of Turkish subpopulations expected to have intermediate- to chronic-duration oral exposures to boron (Sayli 1998a, 1998b, 2003; Sayli et al. 1998), or in surveys of boron mining and processing workers in California (Whorton et al. 1994) and China (Chang et al. 2006). Chronic-duration oral toxicity studies in animals include 2-year toxicity studies in Sprague-Dawley rats and beagle dogs exposed to boric acid or borax in the diet (Weir and Fisher 1972), and a 2-year toxicity and cancer bioassay in B6C3F1 mice (Dieter 1994; NTP 1987). Histopathological examination of a comprehensive set of tissues from exposed and control rats and dogs (brain, pituitary, thyroids, lung, heart, liver spleen, kidneys, adrenals, pancreas, intestines, urinary bladder testes, ovary (rat only), bone, and bone marrow) found no exposure-related non-neoplastic or neoplastic lesions at dose levels up to 6.8 mg boron/kg/day in dogs or 81 mg boron/kg/day in rats, with the exception that rats exposed to 81 mg boron/kg/day, but not 24 mg boron/kg/day, showed testicular atrophy, decreased growth, decreased packed blood cell and hemoglobin levels, and scaly tails and desquamated footpad skin (Weir and Fisher

1972). In the mouse bioassay, no cancer responses were observed at dose levels up to 201 mg boron/kg/day (Dieter 1994; NTP 1987). Noncancer effects in mice included testicular atrophy and interstitial hyperplasia, lung hemorrhage, and 10–17% decreased body weight at 201 mg boron/kg/day and splenic hematopoiesis and chronic hepatic inflammation and coagulative necrosis at 79 and 201 mg boron/kg/day, the only dose levels included in the study.

Although data are sufficient to develop a chronic oral MRL, a value was not derived. Because intermediate-duration LOAELs for developmental toxicity in rats (13.6 and 13 mg boron/kg/day [Heindel et al. 1992; Price et al. 1996a, 1998]) were lower than the NOAEL (24 mg boron/kg/day) for testicular atrophy and other non-cancer effects in chronically exposed rats (Weir and Fisher 1972), the intermediate MRL, which is based on developmental toxicity, should be protective against reproductive toxicity following chronic exposure. In mice, the intermediate-duration oral NOAEL (43.4 mg boron/kg/day) and LOAEL (79 mg boron/kg/day) for developmental toxicity in CD-1 mice (Heindel et al. 1992) were lower than the chronic-duration LOAEL for testicular atrophy and decreased body weight in B6C3F1 mice (201 mg boron/kg/day) and overlapped with the LOAEL (79 mg boron/kg/day) for splenic hematopoiesis and chronic hepatic inflammation and necrosis (Dieter 1994; NTP 1987). Additional studies may be useful in assessing the level of confidence in existing intermediate-duration NOAEL and LOAEL values for developmental toxicity in rats and mice. Additional chronic-duration oral exposure studies in animals do not seem necessary at this time.

As discussed in the previous section, symptoms of acute upper respiratory and ocular irritation have been reported in workers employed in the borax industry for an average of >10 years, but pulmonary function variables were not significantly influenced by exposure over a 7-year period of employment (Garabrant et al. 1984, 1985; Hu et al. 1992; Wegman et al. 1994). These results are the basis of an acute inhalation MRL for boron, but do not clearly indicate whether the dose-response relationships for acute boron-induced upper respiratory and ocular irritation effects are changed with intermediate or chronic durations of exposure. Because exposure-related effects on pulmonary function variables were not evident during a 7-year period of employment, the results provide some confidence that the acute-duration inhalation MRL may by protective for intermediate- and chronic-duration exposures. Additional prospective health evaluations of respiratory function and reproductive and developmental variables in borate mining and processing workers with intermediate- and chronic-duration exposures may help to better identify impaired respiratory function, impaired reproductive performance, and developmental effects as critical effects in humans from intermediate- or chronic-duration inhalation exposure to boron compounds.

The available chronic oral bioassays in rats and dogs exposed to boric acid or borax (Weir and Fisher 1972) and mice exposed to boric acid (Dieter 1994; NTP 1987) found no evidence for exposure-related cancer. Although no epidemiological studies have been conducted to examine possible associations between boron exposure and cancer, the results from the animal studies provide no strong impetus to conduct such studies.

Genotoxicity. No *in vivo* human data were located. Bacterial and limited mammalian assays were negative for mutagenicity (Benson et al. 1984; Landolph 1985; Demerec et al. 1951; Haworth et al. 1983; NTP 1987) or cell transformation (Landolph 1985). However, the *in vivo* animal study of Wery et al. (2003) reported specific genetic alterations in embryos at critical points of development that may be associated with skeletal malformations seen in several animal species. Thus, additional *in vivo* studies may be useful to establish possible dose-response relationships for boron-induced genetic changes and skeletal effects in animals.

Reproductive Toxicity. No associations were found between exposure to borates or boric oxide and indices of fertility in surveys of Turkish subpopulations expected to have intermediate- to chronic-duration oral exposures to boron (Sayli 1998a, 1998b, 2003; Sayli et al. 1998), or in surveys of boron mining and processing workers in California (Whorton et al. 1994) and China (Chang et al. 2006).

Effects on the male and female reproductive organs have been clearly demonstrated in rats orally exposed to boric acid or borax; supporting evidence for effects on the male reproductive organs from oral exposure to boron has been reported in mice and dogs. Testicular atrophy and histopathology, sperm abnormalities, and reduced sperm production have been observed in mice, rats, and dogs after intermediate-duration ingestion of doses ≥26 mg boron/kg/day as boric acid (Dieter 1994; Dixon et al. 1976, 1979; Fail et al. 1991; Fukuda et al. 2000; Harris et al. 1992; Ku et al. 1993a; Kudo et al. 2000; Lee et al. 1978; NTP 1987; Nusier and Bataineh 2005; Seal and Weeth 1980; Weir and Fisher 1972; Yoshizaki et al. 1999). Complete sterility was observed in male and female Sprague-Dawley rats fed boric acid or borax in the diet for 14 weeks before mating at 101 and 116 mg boron/kg/day for males and females, respectively (Weir and Fisher 1972). Sterility was associated with a lack of viable sperm in males and decreased ovulation in females, and no pregnancies occurred when female rats exposed to this dose level were mated with non-exposed male rats. At lower exposure levels (10 or 30 mg boron/kg/day for males and 12 or 35 mg boron/kg/day for females), no exposure-related adverse effects were found on fertility indices in three successive generations (Weir and Fisher 1972). With chronic-duration oral exposure, testicular atrophy occurred at 201, but not 79, mg boron/kg/day in B6C3F1 mice (Dieter 1994; NTP 1987) and at

81, but not 24, mg boron/kg/day in Sprague-Dawley rats (Weir and Fisher 1972). No testicular atrophy was found in dogs exposed for 2 years to dietary doses of boric acid or borax at levels up to 6.8 mg boron/kg/day (Weir and Fisher 1972). In the chronic-duration oral exposure studies, no histologic effects on the ovaries were found in rats (Weir and Fisher 1972) or mice (Dieter 1994; NTP 1987), but the ovaries of chronically exposed female dogs were not examined (Weir and Fisher 1972).

With inhalation exposure to boron compounds, reproductive effects do not appear to be an effect of concern. In intermediate-duration inhalation studies with rats, no histologic effects on the testes or ovaries were found in albino rats exposed to boric oxide aerosols for 6 hours/day, 5 days/week for 10 weeks at an average concentration of 73 mg boron/m^3, 12 weeks at 27 mg boron/m^3, or 24 weeks at 12 mg boron/m^3 (Wilding et al. 1959).

Additional prospective health evaluations of reproductive variables in borate mining and processing workers with intermediate- and chronic-duration exposures may help to better identify impaired reproductive performance as a critical effects in humans from intermediate- or chronic-duration inhalation exposure to boron compounds.

Developmental Toxicity. No studies were found on the developmental effects of boron and compounds in humans following inhalation, oral, or dermal exposure. In acute-duration oral exposure animal studies, developmentally toxic effects (including reduced fetal weight and increased skeletal variations or malformations) have been reported in CD-1 mice exposed during gestation to boric acid doses as low as 70 mg boron/kg (2 times/day) (Cherrington and Chernoff 2002) and in New Zealand rabbits exposed during gestation (days 6–19) to doses of 44 mg boron/kg/day (Price et al. 1996b). Developmental effects (including decreased fetal weight, increased incidence of skeletal variations and malformations, and increased resorptions) have been observed in offspring of rat and mouse dams exposed to 13–79 mg boron/kg/day as boric acid during gestation for intermediate durations (Heindel et al. 1992, 1994; Price et al. 1996a). Developmental effects observed in these animal studies are the critical effects for the acute- and intermediate-duration oral MRLs for boron.

Developmental toxicity studies in animals exposed to boron compounds by inhalation are not available. Such studies may be useful to determine if developmental effects are a critical effect from inhalation exposure to boron compounds.

Immunotoxicity. No studies were found in humans or animals on the effects of boron on the immune system by any route of exposure. Results of chronic studies do not suggest that the immune system is a potential target for boron toxicity. Additional studies are not needed at this time.

Neurotoxicity. Case reports in humans, primarily infants, indicate that neurological effects occur after ingestion of boron at high dose levels (Wong et al. 1964). Degenerative changes in brain cells, perivascular hemorrhage, and intravascular thrombosis have been reported in fatal case reports in infants, but neurochemical or neurophysiological changes have not been reported (Settimi et al. 1982; Wong et al. 1964). No studies are available on neurotoxic effects of boron following inhalation or dermal exposure in humans. Animal data are limited to increased brain enzyme activity (Settimi et al. 1982), but no histopathological data are available. Since data on effects are limited primarily to acute oral exposures at high dose levels, additional studies in animals evaluating other dose levels and exposure routes and durations may be useful in evaluating potential risk to humans who may be exposed to low levels of boron compounds near hazardous waste sites.

Epidemiological and Human Dosimetry Studies. Information exists on the adverse health effects of boron compounds in humans. Symptoms of acute upper respiratory and ocular irritation have been reported in workers employed in the borax industry for an average of >10 years, but pulmonary function variables were not significantly influenced by exposure over a 7-year period of employment (Garabrant et al. 1984, 1985; Hu et al. 1992; Wegman et al. 1994). Corroborative evidence of the irritation potential of airborne boron compounds comes from controlled exposure studies of human volunteers (Cain et al. 2004). No associations were found between exposure to borates or boric oxide and indices of fertility in surveys of Turkish subpopulations expected to have intermediate- to chronic-duration oral exposures to boron (Sayli 1998a, 1998b, 2003; Sayli et al. 1998), or in surveys of boron mining and processing workers in California (Whorton et al. 1994) and China (Chang et al. 2006). Other human studies involve case reports of accidental or intentional ingestion of large quantities of boron compounds (Wong et al. 1964; Litovitz et al. 1988; Locatelli et al. 1987). The case report studies identified key health effects (gastrointestinal, respiratory, renal, neurological, hepatic) associated with boron exposure (Wong et al. 1964).

Results from animal studies indicate that the testes and developing fetus as the most sensitive targets following acute, intermediate, or chronic oral exposure to boron. Epidemiological studies that look for associations between boron exposure and reproductive and/or developmental toxicity end points would be

useful to better identify impaired reproductive performance and developmental effects as critical effects in humans from intermediate- or chronic-duration exposure to boron compounds.

Biomarkers of Exposure and Effect.

Exposure. Blood and urine borate concentrations may be useful biomarkers of exposure (Jansen et al. 1984a; Litovitz et al. 1988). Normal dietary concentrations of boron in the blood of humans range from 0 to 1.25 µg/mL in children and infants (Fisher and Freimuth 1958; O'Sullivan and Taylor 1983). Elevated blood levels of boron have been reported in cases of acute ingestion of boric acid (Linden et al. 1986; Wong et al. 1964). Urinary concentrations of boron in the normal population range from 0.07 to 0.15 mg/100 mL (Vignec and Ellis 1954) and from 0.004 to 0.66 mg/100 mL (Imbus et al. 1963), whereas elevated concentrations have been measured in humans orally exposed to borax or boric acid (Gordon et al. 1973; Jansen et al. 1984a). Additional studies of exposure levels and blood or urinary levels of boron in borate mining and production workers may help to better characterize quantitative relationships between occupational exposure levels and blood or urinary levels of boron.

Effect. The most clearly identified effects in humans exposed to boron compounds are acute respiratory and ocular irritation from acute inhalation exposure to boron compounds. Several other types of effects, including degenerative changes in brain cells, gastrointestinal irritation, degenerative liver or kidney lesions, and skin changes (erythema involving palms, soles, and buttocks), have been observed in some, but not all, cases of acute- or intermediate-duration oral poisoning with boric acid or borax. In orally exposed animals, effects include testicular atrophy in males and decreased ovulation in females, and developmental effects (fetal body weight deficits and skeletal malformations) with gestational exposure. None of these effects, however, are necessarily specific to boron. To date, a specific biomarker of effect for boron has not been developed for humans or animals.

Absorption, Distribution, Metabolism, and Excretion. Limited quantitative information is available on the absorption, distribution, metabolism, and elimination of boron compounds following oral (Dourson et al. 1998; Ku et al. 1991; Moseman 1994; Treinen and Chapin 1991), inhalation (Wilding et al. 1959), and dermal (Draize and Kelley 1959) exposure. Since data on toxicokinetics of boron are limited, additional studies are needed by all routes of exposure that will provide data on absorption rates, amount and rate of accumulation in various tissues, and clearance rates. Limited data from oral and dermal studies suggest that boron is primarily excreted in urine. Since boron can deposit in the upper

respiratory tract, additional excretion studies by this route would be useful in determining if excretion patterns are similar across all routes of exposure.

Comparative Toxicokinetics. Existing evidence from human and animal studies do not indicate whether or not boron compounds affect the same target tissues. Animal studies indicate the testes as a target tissue (Dieter 1994; Dixon et al. 1979; Fukuda et al. 2000; Ku et al. 1993a; Kudo et al. 2000; Lee et al. 1978; NTP 1990; Price et al. 1998; Seal and Weeth 1980; Weir and Fisher 1972). No data have been found on potential reproductive effects of boron and compounds in humans. Data exist on excretion of boron compounds. Based on excretion studies, boron compounds are absorbed by the gastrointestinal tract. There are no available quantitative toxicokinetics data on absorption, distribution, and metabolism. Additional toxicokinetics studies may provide a better basis for extrapolation of animal data to human exposure risk.

Methods for Reducing Toxic Effects. Methods for the mitigation of acute effects of boron poisoning include prevention of absorption of boron from the gastrointestinal tract and standard procedures used to prevent convulsions, severe dehydration, or shock (Stewart and McHugh 1990). Saline diuresis, exchange transfusions, peritoneal dialysis, or hemodialysis may be employed to enhance removal of absorbed boron from the body (Goldfrank et al. 1990; Stewart and McHugh 1990). No additional information was located concerning mitigation of effects of lower-level or longer-term exposure to boron. Further information on techniques to mitigate such effects may be useful in determining the safety and effectiveness of possible methods for treating boron-exposed populations in the vicinity of hazardous waste sites.

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

The comparative susceptibility of children to the acute respiratory and ocular irritation potential of aerosols of boric acid or other boron compounds has not been examined. Results from animal studies indicate that developmental effects associated with gestational exposure are the most sensitive effects associated with acute- or intermediate-duration oral exposures. Degenerative changes in the male (e.g., testicular atrophy and altered spermiation) and female (decreased ovulation) have also been identified as a sensitive effect from boron, but no studies were located that examined the relative susceptibility of young animals (or children) to these effects.

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

3.12.3 Ongoing Studies

Wendie A. Robbins of the University of California Los Angeles is being funded by the NIOSH to perform an epidemiologic study investigating the relationship between workplace exposure to boron-containing compounds (including boric acid, borax) and adverse male reproductive effects. Two published human studies on reproductive effects of occupational boron exposure found no effect on fertility or development, while one study reported positive testicular atrophy and sterility. All three studies have been criticized for inadequacies in study design exposure assessment. The specific aims of this research are to: (1) describe the relationship between boron exposure and direct measures of toxicity on male reproduction, (2) describe the relationship between boron exposure and indirect measures of toxicity on male reproduction, and (3) describe the relationship between workplace, environmental, and dietary sources of boron with biomarkers of exposure and reproductive effect. The goal is to contribute critical information on the exposure level at which boron causes adverse effects on human male reproduction.

4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Boron appears in Group 13 (IIIA) of the periodic table and is the only nonmetal of this group (Jansen 2003). Table 4-1 lists common synonyms, trade names, and other pertinent information to identify boron and selected compounds.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Table 4-2 lists important physical and chemical properties of boron and selected compounds.

Boron is a nonmetal and is typically found in nature bound to oxygen. It is never found as the free element (Cotton et al. 1999). Elemental boron can exist as an amphorous powder and in four crystalline forms: α-rhombohedral, β-rhombohedral, α-tetragonal, and β-tetragonal (Jansen 2003).

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

Characteristic	Boron	Boron oxide	Boric acid
Synonym(s)	Boron, metallic	Boric anhydride; boric acid, anhydride; boron sesquioxide; boron trioxide; diboron trioxide; fused boric acid	Orthoboric acid; boron hydroxide; boron trihydroxide
Registered trade name(s)	No data	No data	Borofax[b]
Chemical formula	B	B_2O_3	$B(OH)_3$
Chemical structure	Amphorous powder, as well as four crystalline forms: α-rhombohedral, β-rhombohedral, α-tetragonal, and β-tetragonal[c]	Randomly oriented B_3O_3 rings with bridging oxygen atoms[d]	Planar BO_3^{3-} units linked by asymmetrical hydrogen bonds[d]
Identification numbers:			
CAS registry	7440-42-8	1303-86-2	10043-35-3
NIOSH RTECS[e]	ED7350000	ED7900000	ED4550000
EPA hazardous waste	No data	No data	No data
EPA/OPP pesticide Code	128945	011002	011001
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMDG shipping	No data	No data	No data
HSDB	4482	1609	1432
EINECS	231-151-2	215-125-8	233-139-2
NCI	No data	No data	C56417

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

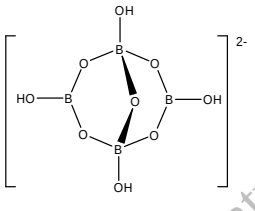
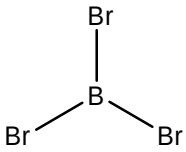
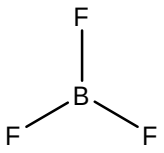
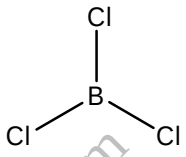
Characteristic	Borax	Sodium tetraborate	Boron tribromide
Synonym(s)	Sodium borate; sodium tetraborate; borax decahydrate; disodium tetraborate decahydrate	Sodium borate; sodium borate anhydrous; disodium tetraborate; sodium biborate; sodium pyroborate; boric acid, disodium salt	Boron bromide; tribromo-borane; tribromoboron
Registered trade name(s)	Jaikin, Pyrobor, Three Elephant, V-Bor[b]	Rasorite 65[b]	No data
Chemical formula	$B_4Na_2O_7 \cdot 10H_2O$	$Na_2B_4O_7$	BBr_3
Chemical structure	 Tetraborate anion in solution[d]	Anhydrous borates have polymeric assemblies of planar BO_3 and/or tetrahedral BO_4 units linked by shared oxygen atoms[d]	
Identification numbers:			
CAS registry	1303-96-4	1330-43-4	10294-33-4
NIOSH RTECS[e]	VZ2275000	ED4588000	ED7400000
EPA hazardous waste	No data	No data	No data
EPA/OPP Pesticide Code	029601	011112	No data
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMDG shipping	No data	No data	UN 2692; IMDG 8.1
HSDB	328	5025	327
EINECS	233-139-2	215-540-4	233-657-9
NCI	No data	No data	No data

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

Characteristic	Boron trifluoride	Boron trichloride
Synonym(s)	Anca 1040; boron fluoride; trifluoroborane	Trichloroborane; trichloroboron
Registered trade name(s)	No data	No data
Chemical formula	BF_3	BCl_3
Chemical structure		
Identification numbers:		
CAS registry	7637-07-2	10294-34-5
NIOSH RTECS[e]	ED2275000	ED1925000
EPA hazardous waste	No data	No data
EPA/OPP Pesticide Code	No data	No data
OHM/TADS	No data	No data
DOT/UN/NA/IMDG shipping	UN 1008; IMDG 6.1 (boron trifluoride); UN 2851; IMDG 8.2 (boron trifluoride dihydrate)	UN 1741; IMDG 2.2
HSDB	325	326
EINECS	231-569-5	233-658-4
NCI	No data	No data

[a]All information obtained from HSDB 2007 and ChemIDplus 2007, except where noted.
[b]NIOSH 2007
[c]Jansen 2003
[d]Cotton et al. 1999
[e]RTECS 2007

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

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

Property	Boron	Boron oxide	Boric acid
Molecular weight	10.811	69.620	61.833
Physical description	Black or dark brown powder (amorphous form); clear red crystals (α-rhombohedral form); black, opaque crystals with metallic luster (α-tetragonal form); black (β-rhombohedral form)	Colorless, glassy or hexagonal crystals, hygroscopic	Colorless, transparent crystals; white granules or powder
Melting point	2,075 °C	450 °C (crystal)	170.9 °C
Boiling point	4,000 °C	1,500 °C (crystal)	No data
Density	2.350 g/cm^3 (amorphous); 2.46 g/cm^3 (α-rhombohedral); 2.31 g/cm^3 (α-tetragonal); 2.35 g/cm^3 (β-rhombohedral)	1.8 g/cm^3 (amorphous); 2.46 g/cm^3 (crystal)	1.435 g/cm^3 at 15 °C
Odor	No data	Odorless	Odorless
Solubility:			
Water	Insoluble	4.0% at 20 °C	50 g/L at 25 °C
Organic solvent(s)	Insoluble alcohol, ether	Soluble in alcohol, glycerol	17.5% in glycerol; 18.5% in ethylene glycol; 173.9 g/L in methanol; 94.4 g/L in ethanol; 0.6% in acetone; 1.5% in ethyl acetate (all at 25 °C)
Other	Soluble in concentrated nitric and sulfuric acids	No data	No data
pK_a	No data	No data	9.42
Log K_{ow}	No data	No data	0.175
Vapor pressure	0.0119 mm Hg at 2,140 °C	Negligible at 20 °C	Negligible at 20 °C
Autoignition temperature	580 °C	No data	No data
Flashpoint	No data	No data	No data
Flammability limits in air	Dust ignites spontaneously in air	Noncombustible	Not flammable
Conversion factors	No data	No data	No data
Explosive limits	No data	No data	No data

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

Property	Borax	Sodium tetraborate	Boron tribromide
Molecular weight	381.373	201.220	250.52
Physical Description	White, monoclinic crystals	Colorless glassy solid; hygroscopic	Colorless, fuming liquid
Melting point	75 °C (decomposes)	743 °C	-46.0 °C
Boiling point	No data	1,575 °C (decomposes)	90 °C
Density	1.73 g/cm^3	2.367 g/cm^3	2.698 g/cm^3 at 0 °C
Odor	Odorless	Odorless	Sharp, irritating odor
Solubility:			
Water	59.3 g/L at 25 °C	3.1% at 25 °C	Decomposes in water
Organic solvents	1 g/1 mL in glycerol; insoluble in alcohol	16.7% in methanol; 30% in ethylene glycol; 40.6 g/L in formamide (all at 25 °C)	Decomposes in alcohol; soluble in carbon tetrachloride, sulfur dioxide (liquid), carbon disulfide
Other	Insoluble in acid	No data	No data
pK_a	No data	No data	No data
Log K_{ow}	No data	No data	No data
Vapor pressure	Negligible	Negligible at 20 °C	100 mm Hg at 33.5 °C
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits in air	Not flammable	Noncombustible	Nonflammable
Conversion factors	No data	No data	1 ppm=10.25 mg/m^{3b}
Explosive limits	No data	No data	No data

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

Property	Boron trifluoride	Boron trichloride
Molecular weight	67.81	117.17
Physical Description	Colorless gas	Colorless fuming liquid at low temperature
Melting point	-126.8 °C	-107 °C
Boiling point	-101 °C	12.5 °C
Density	3.07666 g/L at 1 atm, 0 °C	1.3728 g/cm^3 at 0 °C
Odor	Pungent, suffocating odor[c]	Pungent, suffocating odor
Solubility:		
Water	332 g/100 g water at 0 °C with some hydrolysis forming fluoboric and boric acids	Decomposes in water
Organic solvents	Soluble in benzene, dichlorobenzene, chloroform, carbon tetrachloride, carbon sulfide; soluble in most saturated and halogenated hydrocarbons and in aromatic compounds	Decomposes in alcohol
Other	1.94 g/100 g in anhydrous sulfuric acid	No data
pK_a	No data	No data
Log K_{ow}	No data	No data
Vapor pressure	3.656x10^4 mm Hg at -13.2 °C	1 mm Hg at 25 °C (extrapolated)
Autoignition temperature	No data	No data
Flashpoint	No data	No data
Flammability limits in air	Nonflammable	Nonflammable
Conversion factors	1 ppm=2.77 mg/m^3[b]	No data
Explosive limits	No data	No data

[a]All information from HSDB 2007, except where noted.
[b]NIOSH 2005
[c]Odor threshold 4.50 mg/m^3 (Ruth 1986)

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

5.1 PRODUCTION

Boron is the 51st most common element found in the earth's crust and is found at an average concentration of 8 mg/kg (Cotton et al. 1999; Jansen 2003). Boron is a nonmetal and is typically found in nature bound to oxygen. It is never found as the free element (Cotton et al. 1999). There are over 200 minerals containing boron oxide; however, only four boron-containing minerals, borax, kernite, colemite, and ulexite, comprise the majority, nearly 90%, of the borates used by industry worldwide. These minerals are extracted mainly from California and Turkey. The majority of domestic boron production is from Kern County, California, with the remainder from San Bernardino and Inyo Counties in California (USGS 2007b).

The most widely used commercial process for producing boron is the Moissan process, which involves the reduction of boric oxide with magnesium (Jansen 2003). This process yields 90–92% pure boron, which is then leached with acid to separate it from the magnesium oxide formed during the process, followed by multiple washes and drying. The purity of the boron can be increased to 95–97% by further chemical processing (Jansen 2003). Due to boron's tendency to bind to electron-rich elements (carbon, nitrogen, and oxygen) it can be very difficult to isolate boron in high purity (Cotton et al. 1999). High purity boron (>99.9%) is prepared by the reduction of boron trihalides or by the decomposition of boron triiodide or boron hydrides at high temperatures. Other methods include electrolytic reduction of potassium tetrafluoroborate (KBF_4) in molten potassium chloride-potassium fluoride mixtures. High purity boron can generally only be obtained in kilogram quantities (Cotton et al. 1999).

In 2005, 1.15 million metric tons of boron ore were produced in the United States, with a boron oxide (B_2O_3) content of 612,000 metric tons. Colemanite, kernite, tincal (natural borax), and ulexite were the most common mineral of commercial importance in the United States. Boron compounds and minerals are produced both by surface and underground mining, as well as from brine (USGS 2007b).

Boron trifluoride is prepared by the reaction of a boron-containing material and a fluorine-containing substance in the presence of an acid (e.g., borax, fluorspar, and sulfuric acid) (Alam et al. 2003). It can also be produced by the treatment of fluorosulfonic acid with boric acid. Large-scale production of boron trichloride involves the reaction of chlorine with a mixture of borax and crude oil residue heated in a rotary kiln. On a smaller-scale, boron trichloride can be prepared by reacting chlorine and a mixture of boron oxide, petroleum coke, and lampblack (carbon black) in a fluidized bed. Large-scale production of

boron tribromide involves reaction of bromine and granulated boron carbide (B_4C) at 850–1,000°C or by reaction of hydrogen bromide with calcium boride (CaB_6) at high temperatures (Alam et al. 2003).

Tables 5-1 and 5-2 list facilities in each state that manufacture or process boron trifluoride and boron trichloride, respectively, as well as the intended use and the range of maximum amounts of these boron compounds that are stored onsite. In 2005, there were 47 and 16 reporting facilities that produced, processed, or used boron trifluoride and boron trichloride, respectively, in the United States. The data listed in Tables 5-1 and 5-2 are derived from the Toxics Release Inventory (TRI05 2007). Only certain types of facilities were required to report. Therefore, this is not an exhaustive list. Current U.S. manufacturers of boron and selected boron compounds are given in Table 5-3.

5.2 IMPORT/EXPORT

Turkey was a major import source in 2002–2005 for boric acid, supplying 57%, followed by Chile (31%), Peru (5%), and Russia (3%) (USGS 2007a). In 2005, U.S. imports of borax, boric acid, colemanite, and ulexite were $1x10^3$, $52x10^3$, $31x10^3$, and $103x10^3$ metric tons, respectively. In 2005, U.S. exports of boric acid and refined sodium borates were $183x10^3$ and $308x10^3$ metric tons, respectively (USGS 2007a).

5.3 USE

In 2005, the estimated use distribution pattern for boron compounds in the United States was 70% for glass and ceramics, 5% for soaps and detergents, 4% for fire retardants, and 2% for agriculture, with other uses, including metallurgy, nuclear applications, sale to distributors, and miscellaneous applications, making up the remaining 19% (USGS 2007a). Boric acid is used in cosmetics, pharmaceuticals, and toiletries. It is also used to reduce the flammability of cellulose insulation, cotton batting in mattresses, and wood composites. Boron oxide is incorporated into cellulose materials to inhibit combustion. Borates are used in the manufacture of adhesives and are added to lubricants, brake fluids, metalworking fluids, water treatment chemicals, and fuel additives (USGS 2007b).

Pesticide products containing boric acid and its sodium salts (sodium tetraborate decahydrate, sodium tetraborate pentahydrate, anhydrous sodium tetraborate, disodium octaborate tetrahydrate, anhydrous disodium octaborate, and sodium metaborate) are registered in the United States for use as insecticides, fungicides, and herbicides. There are 189 pesticide products registered that contain boric acid or its sodium salt as an active ingredient. Boric acid and its sodium salts are used on several agricultural and many non-agricultural sites including residential, commercial, medical, veterinary, industrial, forestry,

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

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AL	4	1,000	99,999	2, 3, 6, 10
AR	3	1,000	99,999	2, 3, 6
DE	1	100,000	999,999	1, 4
FL	2	10,000	99,999	6, 10
KY	2	10,000	99,999	10, 12
LA	4	1,000	999,999	2, 3, 10, 11
MD	2	1,000	99,999	6
NJ	1	1,000	9,999	6
NY	3	1,000	999,999	6
OH	1	10,000	99,999	6
OK	2	10,000	999,999	1, 3, 6
PA	7	1,000	999,999	6, 7, 9, 10, 12
SC	4	1,000	99,999	2, 3, 6
TN	1	10,000	99,999	10
TX	10	1,000	999,999	2, 3, 4, 6, 9, 10, 11, 12

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

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

Source: TRI05 2007 (Data are from 2005)

Table 5-2. Facilities that Produce, Process, or Use Boron Trichloride

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AZ	1	100	999	11, 12
CA	1	1,000	9,999	1, 3, 4, 9
IN	3	10,000	999,999	6, 7, 10, 11
MA	1	1,000	9,999	6
MI	1	1,000	9,999	10
NM	2	100	9,999	11
OH	1	1,000	9,999	6
PA	3	1,000	99,999	2, 4, 9
SC	1	1,000	9,999	2, 3, 6, 7, 10, 11
WI	2	1,000	99,999	6

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

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

Source: TRI05 2007 (Data are from 2005)

Table 5-3. Current U.S. Manufacturers of Boron and Selected Boron Compounds

Company	Location
Boron	
Eagle-Picher Industries, Inc., Eagle-Pitcher Technologies, LLC, Boron Department	Quapaw, Oklahoma
SB Boron Corporation	Franklin Park, Illinois
Tronox Incorporated	Henderson, Nevada
Boron oxide	
Johnson Matthey, Inc., Alfa Aesar	Ward Hill, Massachusetts
Boric acid	
InCide® Technologies, Inc.	Phoenix, Arizona
Searles Valley Minerals, Argus-Trona-Westend Complex	Trona, California
U.S. Borax Inc.	Boron, California
Sodium tetraborate decahydrate (Borax decahydrate)	
Searles Valley Minerals, Argus-Trona-Westend Complex	Westend, California
U.S. Borax Inc.	Boron, California
Sodium tetraborate (Borax)	
Searles Valley Minerals, Argus-Trona-Westend Complex	Trona, California Westend, California
U.S. Borax Inc.	Boron, California
Boron tribromide	
Air Liquide America L.P., Air Liquide Electronics Division	Dallas, Texas
Eagle-Picher Industries, Inc., Eagle-Pitcher Technologies, LLC, Environmental Science and Technology Department	Miami, Oklahoma
Schumacher	Carlsbad, California
Boron trifluoride dihydrate	
Atotech USA Inc.	Rock Hill, South Carolina
Boron trichloride	
Tronox Incorporated	Henderson, Nevada

Source: Stanford Research Institute (SRI 2006), except where otherwise noted. SRI reports production of chemicals produced in commercial quantities (defined as exceeding 5,000 pounds or $10,000 in value annually) by the companies listed.

and food/feed handling areas. Various formulations are available, including liquids, soluble and emulsifiable concentrates, granulars, powders, dusts, pellets, tablets, solids, paste, baits, and crystalline rods (EPA 1993).

Boron halides are important industrial chemicals. Their Lewis acid properties make them useful as catalysts. Boron trichloride is widely used to prepare boron filaments by chemical vapor deposition (CVD). Much of the boron tribromide produced in the United States is used in the manufacture of proprietary pharmaceuticals (Alam et al. 2003).

5.4 DISPOSAL

Boron trifluoride and boron trichloride are classified as an extremely hazardous substances under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA), commonly known as Superfund, and the Superfund Amendments and Reauthorization Act (SARA) of 1986 and the Emergency Planning and Community Right-to-Know Act (EPCRA), also known as Title III of SARA. Under CERCLA, spills or discharges into the environment of more than 500 pounds of boron trifluoride or boron trichloride must be reported immediately to the National Response Center (EPA 2007c).

Boron trifluoride and boron trichloride are also regulated under the chemical accident prevention provisions of the Clean Air Act (CAA) amendments of 1990. Owners and operators of stationary sources who produce, process, handle, or store boron trifluoride in excess of 5,000 pounds are required to initiate specific activities to prevent and mitigate accidental releases (i.e., hazard assessment, a prevention program, and an emergency response program) (EPA 2007b).

Boron recycling in the United States during 2005 was insignificant (USGS 2007a). No other information regarding disposal of boron or other boron compounds was located.

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

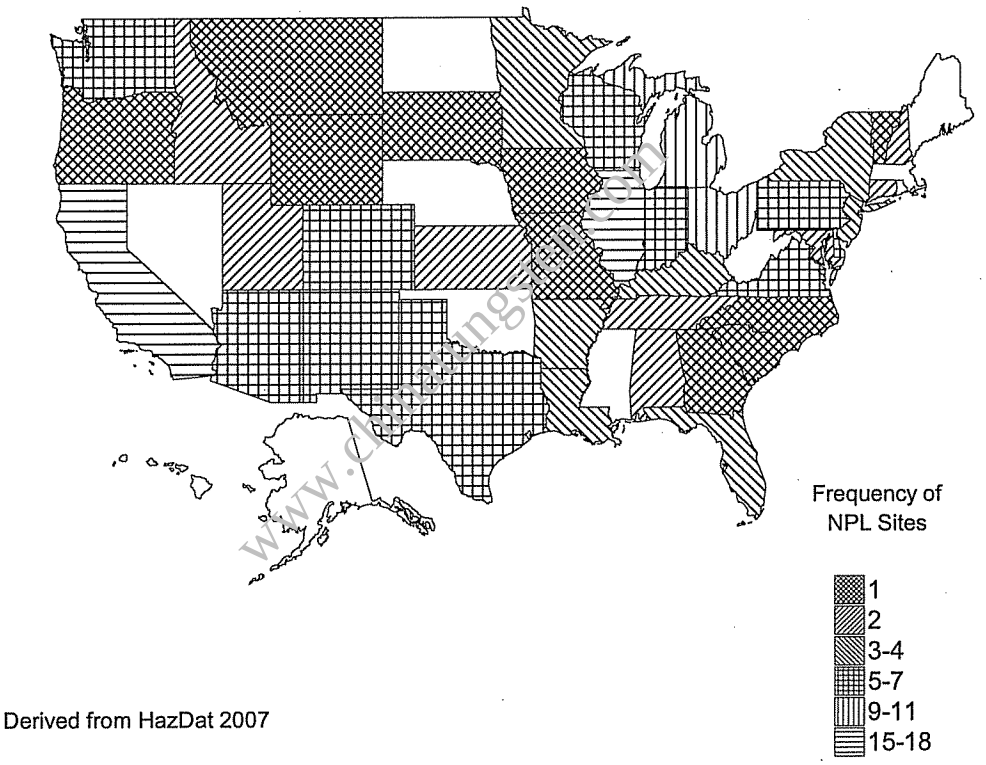
Boron and boron compounds have been identified in at least 164 of the 1,689 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2007). However, the number of sites evaluated for boron and boron compounds is not known. The frequency of these sites can be seen in Figure 6-1. Of these sites containing boron and boron compounds, 163 are located within the United States and 1 is located in Guam (not shown).

Boron is the 51st most common element found in the earth's crust and is found in an average concentration of 8 mg/kg (approximately 0.0008%) (Cotton et al. 1999; Jansen 2003). Boron is a nonmetal and is typically found in nature bound to oxygen. It is never found as the free element (Cotton et al. 1999). There are over 200 minerals containing boron oxide; the four most important boron-containing minerals are borax, kernite, colemite, and ulexite (USGS 2007b). Boron is an essential micronutrient for most plants and there is evidence that it is also essential for animals, including humans (Rainey et al. 1999).

In 2005, the primary use of boron compounds was for glass and ceramics, followed by soaps and detergents, fire retardants, and agriculture (USGS 2007a). Boric acid is used in cosmetics, pharmaceuticals, and toiletries. It is also used to reduce the flammability of cellulose insulation, cotton batting in mattresses, and wood composites. Boron oxide is also incorporated into cellulose materials to inhibit combustion. Borates are used in the manufacture of adhesives and are added to lubricants, brake fluids, metalworking fluids, water treatment chemicals, and fuel additives (USGS 2007b). There are 189 pesticide products registered in the United States that contain boric acid or its sodium salt as an active ingredient (EPA 1993).

Borates are widespread, naturally-occurring substance found mainly as inorganic compounds in sediments and sedimentary rock. Boron is released to the environment slowly in low concentrations by weathering processes. Although few data are available quantifying boron releases from industrial sources, it is estimated that natural weathering releases more boron to the environment worldwide than do these industrial sources (Butterwick et al. 1989).

Figure 6-1. Frequency of NPL Sites with Boron and Selected Boron Contamination



Boron can be released from municipal sewage wastewater, coal-burning power plants, copper smelters, and industries using boron compounds. Boron can also be released from runoff where boron-containing fertilizers and herbicides are used (Butterwick et al. 1989; Fox et al. 2002; Nolte 1988; Waggott 1969).

Adsorption-desorption reactions are expected to be the only significant mechanism that will influence the fate of boron in water (Rai et al. 1986). The extent of boron adsorption depends on the pH of the water and the chemical composition of the soil. The greatest adsorption is generally observed at pH 7.5–9.0 (Keren and Mezuman 1981; Keren et al. 1981; Waggott 1969). The abundance of amorphous aluminum oxide in soil is the single-most important property of soil that will influence the mobility of boron (Bingham et al. 1971).

Rainey et al. (1999) reported mean daily intakes of boron for male and female adults to be 1.17 and 0.96 mg, respectively, from food and beverages. Daily dietary boron intakes of ranging from 0.85 to 0.91 mg were reported for children aged 4–18 years.

Ingestion of boron from food (primarily fruits and vegetables) and water is the most frequent route of human exposure, but occupational exposures to boron dusts may be significant. Boron is also a component of several consumer products, including cosmetics medicines and insecticides. Populations residing in areas of the western United States with natural boron-rich deposits may be exposed to higher-than-average levels of boron.

Boron is widely distributed in surface water and groundwater. An average surface water boron concentration in the United States is about 0.1 mg /L (Butterwick et al. 1989; EPA 1986b), but concentrations vary greatly, depending on boron content of local geologic formations and anthropogenic sources of boron (Butterwick et al. 1989). A survey of U.S. surface waters detected boron in 98% of 1,577 samples at concentrations ranging from 0.001 to 5 mg/L (Butterwick et al. 1989). Concentrations of boron in tap water have been reported in a range of 0.007–0.2 mg/L in the United States, Canada, and England (Choi and Chen 1979; Davies 1990; Waggott 1969). In a 1987 survey of 989 public water supplies, boron concentrations ranged from <0.005 to >2 mg/L (NIRS 1987). Mean boron concentrations in soil in the United States are about 30 mg/kg, with concentrations ranging up to 300 mg/kg (Eckel and Langley 1988; USGS 1984).

6.2 RELEASES TO THE ENVIRONMENT

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

6.2.1 Air

Estimated releases of 6,019 pounds (~2.7 metric tons) of boron trifluoride to the atmosphere from 21 domestic manufacturing and processing facilities in 2005, accounted for about 100% of the estimated total environmental releases from facilities required to report to the TRI (TRI05 2007). No releases of boron trichloride to the atmosphere in 2005 were reported from three domestic manufacturing and processing facilities required to report to the TRI (TRI05 2007). These releases for boron trifluoride and boron trichloride are summarized in Tables 6-1 and 6-2, respectively. There is no information on releases of other boron compounds to the atmosphere from manufacturing and processing facilities because these releases are not required to be reported (EPA 1997).

Borates are released to air from natural and industrial sources. Natural sources include oceans, volcanoes, and geothermal steam (Graedel 1978). Boron compounds are released from anthropogenic sources such as coal-fired and geothermal steam power plants, chemical plants, and rockets as well as manufacturing facilities producing fiberglass and other products (EPA 1987c; Graedel 1978; Hollis et al. 1988; Lang et al. 1986; Rope et al. 1988; Stokinger 1981).

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

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AR	1	10	0	0	0	0	10	0	10
DE	1	1,673	0	0	0	0	1,673	0	1,673
FL	1	0	0	0	0	0	No data	0	0
LA	3	11	0	0	0	0	11	0	11
MD	1	52	0	0	0	0	52	0	52
OK	1	226	0	0	0	0	226	0	226
PA	3	2,445	0	0	0	0	2,445	0	2,445
SC	1	0	0	0	0	0	No data	0	0
TX	9	1,602	0	0	0	0	1,602	0	1,602
Total	21	6,019	0	0	0	0	6,019	0	6,019

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

RF = reporting facilities; UI = underground injection

Source: TRI05 2007 (Data are from 2005)

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

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
MA	1	0	0	0	0	0	0	0	0
NV	1	No data	No data	No data	No data	No data	No data	No data	No data
OH	1	0	0	0	0	0	0	0	0
Total	3	0	0	0	0	0	0	0	0

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

RF = reporting facilities; UI = underground injection

Source: TRI05 2007 (Data are from 2005)

Boron or boron compounds have been identified in 1 air sample collected from 1,689 current or former NPL hazardous waste sites where it was detected in some environmental media (HazDat 2007).

6.2.2 Water

No releases of boron trifluoride or boron trichloride to surface water were reported from 21 and 3 domestic manufacturing and processing facilities, respectively, in 2005 (TRI05 2007). Releases for boron trifluoride and boron trichloride are summarized in Tables 6-1 and 6-2, respectively. There is no information on releases of other boron compounds to surface water from manufacturing and processing facilities because these releases are not required to be reported (EPA 1997).

Boron compounds are released to water in municipal sewage from perborates in detergents, and in waste waters from coal-burning power plants, copper smelters, and industries using boron. Borate levels above background may be present in runoff waters from areas where boron-containing fertilizers or herbicides were used (Butterwick et al. 1989; Nolte 1988; Waggott 1969). An average boron concentration of 1 mg/L was reported in sewage effluents in California (Butterwick et al. 1989). Waggott (1969) reported that boron concentrations in municipal sewage in a treatment plant in England ranged from 2.5 to 6.5 mg/L, releasing between 130 and 240 kg boron/day. Matthijs et al. (1999) reported boron concentrations of 0.41–1.2, 0.39–0.96, and 0.44–1.0 mg/L in raw sewage, settled sewage, and effluent, respectively, collected in 1994 from seven Dutch sewage treatment plants. These data demonstrate that boron passes through the sewage treatment process virtually unchanged. Since boron cannot be degraded and is not substantially absorbed during processing, there is almost no removal during the sewage treatment process (Fox et al. 2002).

Boron or boron compounds have been identified in 100 groundwater and 57 surface water samples collected from 1,689 NPL hazardous waste sites, where it was detected in some environmental media (HazDat 2007).

6.2.3 Soil

No releases of boron trifluoride or boron trichloride to soil or by underground injection were reported from 21 and 3 domestic manufacturing and processing facilities, respectively, in 2005 (TRI05 2007). These releases for boron trifluoride and boron trichloride are summarized in Tables 6-1 and 6-2, respectively. There is no information on releases of other boron compounds to soil or by underground

injection from manufacturing and processing facilities because these releases are not required to be reported (EPA 1997).

Boron is naturally released to soil and water by rainfall, weathering of boron-containing minerals, desorption from clays, and decomposition of boron-containing organic matter. Human-made sources include application of boron-containing fertilizers or herbicides, application of fly ash or sewage sludge as a soil amendment, the use of waste water for irrigation, or land disposal of boron-containing industrial wastes (Butterwick et al. 1989; Hollis et al. 1988; Mumma et al. 1984; Nolte 1988; Rope et al. 1988). Mumma et al. (1984) reported that the boron concentration in sewage sludges from 23 U.S. cities ranged from 7.1 to 53.3 mg/kg. Landfilling or land application is a common disposal method for these sludges.

Boron or boron compounds have been identified in 37 soil and 21 sediment samples collected from 1,689 NPL hazardous waste sites, where it was detected in some environmental media (HazDat 2007).

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

Boron is generally found in nature bound to oxygen and is never found as the free element (Cotton et al. 1999). Atmospheric boron may be in the form of particulate matter or aerosols as borides, boron oxides, borates, boranes, organoboron compounds, trihalide boron compounds, or borazines. Borates are relatively soluble in water, and will probably be removed from the atmosphere by precipitation and dry deposition (EPA 1987c). The half-life of airborne particles is usually on the order of days, depending on the size of the particle and atmospheric conditions (Nriagu 1979). No specific information on the fate of atmospheric boron was located.

Boron readily hydrolyzes in water to form the electrically neutral, weak monobasic acid boric acid (H_3BO_3) and the monovalent ion, $B(OH)_4^-$. In concentrated solutions, boron may polymerize, leading to the formation of complex and diverse molecular arrangements. Rai et al. (1986) concluded that because most environmentally relevant boron minerals are highly soluble in water, it is unlikely that mineral equilibria will control the fate of boron in water. Boron was found to not be significantly removed during the conventional treatment of waste water (Matthijs et al. 1999; Pahl et al. 2001; Waggott 1969). Boron may, however, be co-precipitated with aluminum, silicon, or iron to form hydroxyborate compounds on the surfaces of minerals (Biggar and Fireman 1960).

Waterborne boron may be adsorbed by soils and sediments. Adsorption-desorption reactions are expected to be the only significant mechanism that will influence the fate of boron in water (Rai et al. 1986). The extent of boron adsorption depends on the pH of the water and the chemical composition of the soil. The greatest adsorption is generally observed at pH 7.5–9.0 (Keren and Mezuman 1981; Keren et al. 1981; Waggott 1969). Bingham et al. (1971) concluded that the single most important property of soil that will influence the mobility of boron is the abundance of amorphous aluminum oxide. The extent of boron adsorption has also been attributed to the levels of iron oxide (Sakata 1987), and to a lesser extent, the organic matter present in the soil (Parks and White 1952), although other studies (Mezuman and Keren 1981) found that the amount of organic matter present was not important.

The adsorption of boron may not be reversible in some soils. The lack of reversibility may be the result of solid-phase formation on mineral surfaces (Rai et al. 1986) and/or the slow release of boron by diffusion from the interior of clay minerals (Griffin and Burau 1974).

Partition coefficients such as adsorption constants describe the tendency of a chemical to partition from water to solid phases. Adsorption constants for inorganic constituents such as boron cannot be predicted *a priori*, but must be measured for each soil-water combination. Compilations of available data for boron are given elsewhere (Rai et al. 1986). In general, boron adsorption will be most significant in soils that contain high concentrations of amorphous aluminum and iron oxides and hydroxides such as the reddish Ultisols in the southeastern United States.

It is unlikely that boron is bioconcentrated significantly by organisms from water. A bioconcentration factor (BCF) relates the concentration of a chemical in the tissues of aquatic and terrestrial animals or plants to the concentration of the chemical in water or soil. The BCFs of boron in marine and freshwater plants, fish, and invertebrates were estimated to be <100 (Thompson et al. 1972). Experimentally measured BCFs for fish have ranged from 52 to 198 (Tsui and McCart 1981). These BCFs suggest that boron is not significantly bioconcentrated.

6.3.2 Transformation and Degradation

6.3.2.1 Air

There is no information available that suggests that particulate boron compounds are transformed or degraded in the atmosphere. Particulate-phase boron compounds would be removed from the atmosphere

by wet and dry deposition. Volatile boron trihalides are moisture sensitive and will hydrolyze to boric acid and their corresponding halogen acid (Culver et al. 1994b).

6.3.2.2 Water

As an element, boron itself cannot be degraded in the environment; however, it may undergo various reactions that change the form of boron (e.g., precipitation, polymerization, and acid-base reactions) depending on conditions such as its concentration in water and pH. In nature, boron in generally found in its oxygenated form (Cotton et al. 1999). In aqueous solution, boron is normally present as boric acid and borate ions, with the dominant form of inorganic boron in natural aqueous systems as undissociated boric acid (Choi and Chen 1979). Boric acid acts as an electron acceptor in aqueous solution, accepting an hydroxide ion from water to form $(B(OH)_4)^-$ ion. In dilute solution, the favored form of boron is $B(OH)_4^-$ (Cotton et al. 1999). In more concentrated solutions (>0.1 M boric acid) and at neutral to alkaline pH (6–11), polymeric species are formed (e.g., $B_3O_3(OH)_4^-$, $B_5O_6(OH)_4^-$, $B_3O_3(OH)_5^{2-}$, and $B_4O_5(OH)_4^{2-}$) (Choi and Chen 1979; Cotton et al. 1999).

6.3.2.3 Sediment and Soil

Most boron compounds are transformed to borates in soil due to the presence of moisture. Borates themselves are not further degraded in soil. However, borates can exist in a variety of forms in soil (see Section 6.2.3). Borates are removed from soils by water leaching and by assimilation by plants.

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

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

6.4.1 Air

Boron concentrations in ambient air samples have been reported to range from $<5x10^{-7}$ to $8x10^{-5}$ mg/m^3, with an average concentration of $2x10^{-5}$ mg/m^3 (Howe 1998). Bertine and Goldberg (1971) estimated that approximately 11,600 tons of boron are injected into the atmosphere as a component of fly ash produced by coal combustion, which was estimated to contain an average boron concentration of about 75 mg/kg. Mean dust concentrations ranging from 3.3 to 18 mg particulates/m^3 were measured in air samples from U.S. facilities where borax was packaged and shipped (Culver et al. 1994a). Dust samples in these facilities were predominantly composed of various types of borates and ranged from 11.8 to 15.2% boron by weight.

6.4.2 Water

Boron is widely distributed in surface water and groundwater. The average surface water boron concentration in the United States is about 0.1 mg/L (Butterwick et al. 1989; EPA 1986b), but concentrations vary greatly, depending on boron content of local geologic formations and anthropogenic sources of boron (Butterwick et al. 1989). A survey of U.S. surface waters detected boron in 98% of 1,577 samples at concentrations ranging from 0.001 to 5 mg/L. Mean boron concentrations calculated for the 15 drainage basins in the continental United States ranged from 0.019 mg/L in the Western Great Lakes Basin to 0.289 mg/L in the Western Gulf Basin (Butterwick et al. 1989). Mean boron concentration ranging from 0.28 to 7.8 mg/L were reported in samples collected during 1985–2002 from 26 sites in the San Joaquin River, California (Hall et al. 2004). The concentration of boron in sea water is about 4.5 mg/L (Butterwick et al. 1989; EPA 1986b).

Several studies have measured boron concentrations in water in those areas of California with boron-rich deposits. Reported high boron concentrations in surface waters ranged from 15 mg/L in coastal drainage waters to 360 mg/L in a boron-rich lake (Butterwick et al. 1989; Deverel and Millard 1988). Mean boron concentration in a California river ranged from 0.30 to 0.50 mg/L over a 20-year period (Butterwick et al. 1989). Reported boron concentrations in groundwater in the San Joaquin Valley ranged from 0.14 to 120 mg/L with a median concentration of about 4 mg/L (Butterwick et al. 1989; Deverel and Millard 1988). Waggott (1969) reported that groundwater boron concentrations >100 mg/L are common in California.

Drinking water surveys generally do not report boron concentration. Concentrations of boron in tap water have been reported in a range of 0.007–0.2 mg/L in the United States and England (Choi and Chen 1979;

Waggott 1969), and the National Inorganics and Radionuclides Survey completed in 1987 reported relatively widespread occurrence of boron in 989 public water supplies (NIRS 1987). Boron concentrations ranged from <0.005 to >2 mg/L, with concentrations of up to 0.4 mg/L in 90% of systems (NIRS 1987). A survey of 969 public water supply systems showed 99% contained boron at <1 mg/L. The maximum level measured was 3.28 mg/L (McCabe et al. 1970). Davies (1990) reported an average boron concentration of 0.0258 mg/L in drinking water from Toronto, Canada (1978–1984).

6.4.3 Sediment and Soil

Background boron levels in U.S. soils were reported at a geometric mean concentration of 26 mg/kg with a maximum concentration of 300 mg/kg (Eckel and Langley 1988). Similar concentrations were reported in a U.S. Geological Survey report (USGS 1984), with an average boron concentration of 33 mg/kg (range <20–300 mg/kg) in surface soils from the conterminous United States. Mean boron concentrations in soil collected in the summer of 1981 from the Idaho National Engineering Laboratory and a reference site were 10.1 and 4.7 mg/kg dry weight, respectively (Rope et al. 1988). A geometric mean boron concentration of 8.98 mg/kg (range 2.90–38.0 mg/kg) was reported in soil collected from Aviles, northern Spain (Ordonez et al. 2003).

Boron is an essential nutrient for plants. Boron soil concentrations for optimum plant growth reportedly range from 0.1 to 0.5 mg/kg for several plant species (Butterwick et al. 1989).

Geometric mean boron concentration in sediment collected in 1993 and 1994 from 16 Great Lake embayments and riverine environments of eastern Lake Erie, southern Lake Ontario, and the Niagara River ranged from 0.5 to 7.9 mg/kg dry weight (Lowe and Day 2002). Boron concentrations in sediments collected in 1992 from the Neosho River Basin in Kansas ranged from 2 to 6.5 mg/kg dry weight (Allen et al. 2001).

6.4.4 Other Environmental Media

Boron concentrations in various foods are summarized in Table 6-3. Rainey et al. (1999) reported the highest content of boron in foods such as raisins, peanut butter, and peanuts, with concentrations of 2.20, 1.45, and 1.70 mg/100 g food, respectively. The top two items that contribute to boron intake were coffee and milk, due to the volume with which they are consumed (Rainey et al. 1999). Hunt et al. (1991) determined boron concentrations various foods. In general, boron concentrations were lowest in foods such as meats, cereal and grain products, and confections, ranging from ≤0.015 mg/kg in many of these

Table 6-3. Boron Levels in Food

Food item	Level (µg/100 g)
Fruits and vegetables	
Apples, raw	360
Applesauce, unsweetened	280
Bananas, raw	135
Beans, string, cooked	120
Broccoli, boiled	250
Cantaloupe, raw	180
Carrots, raw or frozen	140
Coleslaw with dressing	120
Corn, yellow, cooked	46
Fruit cocktail, canned in heavy syrup	240
Grapes, raw	490
Lettuce, raw	105
Onions, raw	190
Oranges, raw	260
Peaches, raw	530
Pears, raw	280
Peas, green, cooked	130
Raisins	2,200
Spinach, boiled	180
Tomatoes, raw	63
Beverages	
Apple juice	180
Beer	12
Coffee, from ground beans	29
Fruit-flavored drink from powder	16
Grape juice unsweetened	300
Milk, whole	18
Orange juice	72
Soft drink, cola-type	13
Tea, leaf, brewed	9
Wine, table, dry	610

Table 6-3. Boron Levels in Food

Food item	Level (µg/100 g)
Meat/fish products	
Beef and vegetable stew	120
Beef vegetable soup with potato, stew type	140
Chicken breast, broiled, without skin	27
Chili con carne, with beans	170
Hamburger, with tomato and/or ketchup	51
Tuna, canned, water packed	54
Other	
Beans, lima, dry cooked, fat added	370
Beans, refried	400
Bran flakes with raisins	450
Bread, white	46
French fries, from frozen, deep fried	110
Ice cream, regular, not chocolate	22
Peanut butter	1,450
Peanuts, roasted, salted	1,700
Peas, black-eyed, cooked, fat added	65
Pizza with meat, thin crust	490
Potato chips	325
Rice, white, cooked	32
Spaghetti sauce	120
Spaghetti with meat sauce	65

Source: Rainey et al. 1999

foods to 1.470 mg/kg in grape jelly. Fruits, vegetables, herbs, and spices contained the highest concentrations of boron, including parsley flakes (26.878 mg/kg), ground cinnamon (10.370 mg/kg); dried onion flakes (6.573 mg/kg), and applesauce (2.828 mg/kg). Meacham and Hunt (1994) studied the boron content in infant (6–11 months) foods. Foods containing fruit typically had the highest concentrations of boron: for example: prunes with tapioca (2.6 mg/kg); apples with ham (2.5 mg/kg); applesauce with apricot (2.5 mg/kg); pears (1.9 mg/kg); and applesauce (1.8 mg/kg).

Minoia et al. (1994) determined the concentrations of various elements in beverages available in Italy. Mean boron concentrations in wine, mineral water, beer, ready-to-drink-infusion of tea, and instant coffees were 1.164, 0.112, 0.166, 0.219, and 0.085 mg/L, respectively. In this study, it was estimated that beverages contributed 34% to the estimated weekly total dietary intake of 9 mg of boron (Minoia et al. 1994).

Boric acid, anhydrous sodium tetraborate, and sodium tetraborate decahydrate (borax) are found in various commercial products including pesticides, plant foods, household cleaners, laundry detergents, facial creams and cleaners, shampoo, diaper rash ointments, and pet products. Typical amounts of borax in detergents range from 1 to 5%. Boric acid concentrations in various ant and roach pesticide products range from 5 to 100% (NIH 2004).

Gonzales et al. (2004) determined elements found in dust collected from homes of Native Americans in Zuni Pueblo, New Mexico where jewelry was produced. Surface dust samples were collected from work and living areas of jewelers' homes and from control homes. A surface area of 715 cm^2 was wiped at each location. Mean boron concentrations were found to be significantly higher in work areas (0.87 µg/sample) than in living areas (0.28 µg/sample) of homes where jewelry was made. The geometric mean boron concentration was 0.19 µg/sample in living areas of homes in which no jewelry was made (Gonzales et al. 2004).

The geometric mean boron concentration in soft tissues of zebra mussels collected in 1993 and 1994 from 16 Great Lake embayments and riverine environments of eastern Lake Erie, southern Lake Ontario, and the Niagara River ranged from 0.92 to 6.89 µg/g dry weight (Lowe and Day 2002). Boron was not detected (detection limit 2–4 µg/g dry weight) in the soft tissues of mussels collected in 1991 or in fish composites collected in 1990–1992 from the Neosho River Basin in Kansas (Allen et al. 2001).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Human exposure to borates may occur through ingestion of food and water or insecticides used to control cockroaches, inhalation of boron-containing powders or dusts, or the use of boron from cosmetics or medical preparations. The most appreciable boron exposure to the general population is likely to be ingestion of food and to a lesser extent in water (Beyer et al. 1983; Waggott 1969). As boron is a natural component of the environment, individuals will have some exposure from foods and drinking water.

Dietary intake of boron in children and adults in the United States is summarized in Table 6-4. Rainey et al. (1999) reported mean daily intakes of boron for male and female adults to be 1.17 and 0.96 mg/day, respectively (range 0.02–>9 mg/day). The highest median boron intake of 1.30 mg/day was found for adult male vegetarians, and the lowest median boron intake of 0.72 mg/day was found for women aged 19–30 years. Median boron intakes were higher in adult male and female vegetarians, 1.47 and 1.29 mg/day, respectively, than for all adult males and females, 1.17 and 0.96 mg/day, respectively (Rainey et al. 1999). Consumption of fruits and vegetables contribute largely to boron intake in the human diet. An average daily intake of 1 mg was reported for boron for individuals in the United States. Consumption of wine may contribute an additional 3–4 mg/day of boron (Pahl et al. 2001).

Concentrations of various elements were determined in hair samples from women in two areas (acid and alkaline) of southern Sweden (Rosborg et al. 2003). Median boron concentrations were 281 and <1 mg/kg in hair samples from the acid and alkaline areas, respectively. In this study, the boron levels in drinking water were similar, 10.6 and 9.3 µg/L, in the acid and alkaline areas, respectively, and the authors noted that drinking water did not explain the significantly higher concentrations of boron in the individuals living in the acid area (Rosborg et al. 2003). A mean boron concentration of 0.50 mg/kg wet weight was reported in lung tissue collected from 26 nonsmoking individuals, aged >50 years with no history of occupational exposure to elements living in Terni, central Italy (Alimonti et al. 1992). Boron was not detected in a national survey of human adipose tissue (EPA 1986c).

Occupational exposure to boron compounds may be higher. Workers in other industries, including manufacture of fiberglass and other glass products, cleaning and laundry products, fertilizers, pesticides, and cosmetics, may also be exposed to boron compounds (Stokinger 1981). Culver et al. (1994a) reported end-of-shift boron concentrations in blood and urine of 0.11–0.26 µg/g and 3.16–10.72 µg/mg creatinine, respectively, collected from workers at a facility where borax is packaged and shipped. An

Table 6-4. Dietary Boron Intake

Age group	Mean±standard deviation (mg/day)
School aged male and female children	
4–8 years (n=993)	0.85±0.040
9–13 years (n=943)	0.91±0.45
14–18 years (n=759)	0.88±0.47
Adult males (≥19 years) (n=3,433)	1.17±0.65
19–30 years (n=878)	1.07±0.64
31–50 years (n=1,297)	1.17±0.64
51–70 years (n=884)	1.28±0.67
>70 years (n=374)	1.19±0.61
Vegetarian (n=49)	1.47±0.70
Adult females (≥19 years) (n=4,881)	0.96±0.55
19–30 years (n=1,199)	0.86±0.55
31–50 years (n=1,734)	0.96±0.55
51–70 years (n=1,220)	1.05±0.55
>70 years (n=728)	0.97±0.52
Vegetarian (n=130)	1.29±1.12
Pregnant women (n=130)	1.01±0.72

Source: Rainey et al. 1999

average boron concentrations in blood and urine collected Monday morning prior to the first shift of the week were 0.09 µg/g and 2.75 µg/mg creatinine, respectively (Culver et al. 1994a).

Workers in other industries, including manufacture of fiberglass and other glass products, cleaning and laundry products, fertilizers, pesticides, and cosmetics, may also be exposed to boron compounds (Stokinger 1981). Reported concentrations of borax dust in different areas of a large borax mining and refining plant ranged from 1.1 to 14.6 mg/m^3 for total particulate (Garabrant et al. 1985) and the mean boric acid/boron oxide dust concentration in a boric acid manufacturing plant was 4.1 mg/m^3 for total particulate (Garabrant et al. 1984). Mean dust concentrations ranging from 3.3 to 18 mg particulates/m^3 were measured in air samples from U.S. facilities where borax was packaged and shipped (Culver et al. 1994a). Dust samples in these facilities were predominantly composed of various types of borates and ranged from 11.8 to 15.2% boron by weight. In another study of dust concentrations in air samples from a U.S. borax production facility, mean total dust concentrations ranged from 0.29 to 18.95 mg particulates/m^3, with average percent boron contents in dust ranging from 5.6 to 10.1% (Woskie et al. 1994).

NIOSH estimated that the number of workers potentially exposed to boron increased from 6,500 in the early 1970s (NOHS 1989) to 35,600 in the early 1980s (NOES 1989). Neither the National Occupational Hazard Survey (NOHS) nor the National Occupational Exposure Survey (NOES) databases contain information on the frequency, concentration, or duration of exposures of workers to any of the chemicals listed therein. These surveys provide only estimates of the number of workers potentially exposed to chemicals in the workplace. Sittig (1985) reports that NIOSH estimated that the numbers of workers potentially exposed to borax, boron oxide, and boron trifluoride are 2,490,000, 21,000, and 50,000, respectively.

6.6 EXPOSURES OF CHILDREN

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

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk

or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

Exposure to boron for children will be similar to adults and will occur primarily through the diet. As boron is a natural component of the environment, children, as with the general population, will have some exposure from foods and drinking water. Rainey et al. (1999) reported daily boron intakes of 0.85, 0.91, and 0.88 mg in 4–8-, 9–13-, and 14–18-year-old male and female children, respectively. A daily boron intake of 1.01 mg was reported for pregnant women. Dietary intake of boron in children in the United States is summarized in Table 6-4. Meacham and Hunt (1994) reported a daily intake of 0.333 mg for infants (6–11 months) from baby foods and beverages.

Children and infants may be exposed to boric acid or its sodium salts in homes where pesticide products containing boric acid or its sodium salts are used. Individuals applying these products in residential setting should take appropriate precautions to avoid exposing children.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

The populations living in areas of California and other western states with boron-rich geological deposits have potentially high exposure to boron from drinking water and locally grown foods (Butterwick et al. 1989). Individuals using boron-containing cosmetics or medicines extensively, especially on damaged skin, may be exposed to higher-than-normal levels of boron (Beyer et al. 1983). Workers in industries producing or using boron-containing materials also have potentially high exposure as noted above (Section 6.5). People living in the vicinity of waste sites are also at risk of higher-than-normal exposure levels.

6.8 ADEQUACY OF THE DATABASE

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

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

6.8.1 Identification of Data Needs

Physical and Chemical Properties. Table 4-2 summarizes many of the relevant physical and chemical properties of boron and selected boron compounds. There are adequate data for the physical and chemical properties of boron and boron compounds. No data needs are identified.

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The TRI, which contains this information for 2005, became available in May of 2007. This database is updated yearly and should provide a list of industrial production facilities and emissions.

Current data on the production volume and uses of boron and boron compounds are available and no further production data are necessary at this time (Alam et al. 2003; USGS 2007a, 2007b); however, a data need exists for disposal methods of boron containing wastes.

Environmental Fate. The only quantifiable mechanism that influences the fate of boron is soil adsorption (Rai et al. 1986). A data need exists for the adsorption and mobility of boron in soils low in aluminum oxide since aluminum oxide content of soils is an important property of soil that will influence the mobility of boron (Bingham et al. 1971).

Bioavailability from Environmental Media. Boron compounds can be absorbed following inhalation of contaminated workplace air, ingestion of contaminated food, or through damaged skin (Draize and Kelley 1959; Wong et al. 1964). The most significant routes of exposure near hazardous waste sites are likely to be through drinking boron-contaminated water and ingestion of locally grown food (Beyer et al. 1983; Butterwick et al. 1989). A data need exists for the amount of boron that is bioavailable from environmentally relevant media, such as drinking water, food, and soil.

Food Chain Bioaccumulation. Only one study was located where boron bioconcentration was actually measured (Tsui and McCart 1981). Future research may be helpful, but it appears that boron is not significantly bioconcentrated. There are no data on the biomagnification of boron in the food chain, but it is not likely that bioaccumulation is a major environmental concern. Therefore, there are no data needs at this time.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of boron in contaminated media at hazardous waste sites are needed so that the information obtained on levels of boron in the environment can be used in combination with the known body burden of boron to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Data on boron levels in surface water and soil are available (Butterwick et al. 1989; Eckel and Langley 1988; EPA 1986b; Hall et al. 2004; Ordonez et al. 2003; Rope et al. 1988; USGS 1984). Data on boron concentration in drinking water are limited (Choi and Chen 1979; Davies 1990; McCabe et al. 1970; NIRS 1987; Waggott 1969). Boron concentrations in foods and beverages have been reported (Hunt et al. 1991; Minoia et al. 1994; Rainey et al. 1999). Additional data on boron concentrations in air, and food, and more recent data on boron concentrations in drinking water would be useful in estimating the exposure of humans to boron.

Exposure Levels in Humans. Background levels of boron in human blood, urine, and hair have been reported (Alimonti et al. 1992; Culver et al. 1994a; Rosborg et al. 2003; Stokinger 1981). Additional data on blood and/or urine concentrations in individuals with potentially high exposure to boron would be useful in assessing the magnitude of human exposure.

This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Children are exposed to boron by the same routes as adults. Rainey et al. (1999) reported daily boron intakes of 0.85, 0.91, and 0.88 mg in 4–8-, 9–13-, and 14–18-year old male and female children, respectively. Meacham and Hunt (1994) reported a daily intake of 0.333 mg for infants (6–11 months) from baby foods and beverages. There do not appear to be any childhood-specific means to decrease exposure to boron.

A data need exists to determine current boron concentrations in breast milk or infant formulas. Continued monitoring of the daily intake of boron in children and infants would be useful in estimating the exposure of this population to boron.

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

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

6.8.2 Ongoing Studies

No ongoing studies pertaining to the environmental fate of boron or boron compounds were identified in a search of the Federal Research in Progress database (FEDRIP 2007).

7. ANALYTICAL METHODS

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

7.1 BIOLOGICAL MATERIALS

Methods for the determination of boron in biological materials are summarized in Table 7-1. Methods for the determination of boron in samples of toxicological interest have been summarized (Stokinger 1981; Van Ormer 1975). Total boron is usually determined after the material is digested or ashed. No techniques are available to quantitatively analyze for specific boron compounds in biological matrices (Culver et al. 1994a). The most common analytical procedure to analyze boron in biological materials involves digestion of the sample in hot acid or base, followed by analysis of the resulting solution by inductively coupled plasma-atomic emission spectrometry (ICP-AES) (Culver et al. 2001).

Goullé et al. (2005) assessed inductively coupled plasma–mass spectrometry (ICP-MS) for detecting metals and metalloids in whole blood, plasma, urine, and hair. ICP-MS is a fast, sensitive method that requires a small sample size. Analysis required 0.4 mL of blood, plasma, or urine and 25 mg of hair. Usuda et al. (1998) noted that boron levels in urine can be influenced by dietary intake of boron and recommended that the intake of large amounts of boron-rich foods or drinks should be avoided if the boron status is being evaluated for possible environmental- or labor-related exposure.

Colorimetric analysis can also be used to determine boron concentrations in biological samples; however, colorimetric procedures are more time-consuming and require more laboratory care and technical skill (Culver et al. 2001). Spectrophotometric methods suffer from interferences from other elements (e.g., Al, Cu, Fe, Zn, and Mo), as well as pH (Sah and Brown 1997).

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urine	Dilution; direct analysis	ICP-AES	6.24 µg/L	100.8–104.2%	Usuda et al. 1998
Whole blood, plasma, urine	Dilution with purified water, acid, buffer, and butanol	ICP-MS	1.33 µg/L (blood) 1.26 µg/L (plasma) 0.25 µg/L (urine)	No data	Goullé et al. 2005
Hair	Mineralization after decontamination with water/acetone	ICP-MS	0.14 ng/mg	No data	Goullé et al. 2005
Blood	Ashed by oxygen in a Parr bomb, dissolved	Colorimetric carmine method	<100 µg/L	84% at 5 µg/mL	Hill and Smith 1959
Serum (borate)	Deproteinized, allowed to react with reagent	Colorimetric carmine method	Greater than endogenous levels, which are <20 mg/L	92–104%	Baselt 1988

ICP-AES = inductively coupled plasma–atomic emission spectroscopy; ICP-MS = inductively coupled plasma–mass spectrometry

Neutron activation analysis (NAA) is another analytical technique used to determine boron in biological samples. In NAA, the sample is bombarded with neutrons, and the element of interest is made radioactive. The amount of the element present in the sample is then determined by measurement of the radioactivity or radioactive decay products. This process involves ^{10}B, which is a naturally occurring, stable isotope of boron that occurs with about 20% abundance. When ^{10}B is bombarded with neutrons, it does not become radioactive, but results in a neutron-capture reaction, resulting in the emission of an α-particle and γ-photon. NAA methods for boron determination are based on the measurement of one of more of the products (α-particle and γ-photon), using techniques such as neutron activation mass spectrometry (NA-MS) or prompt γ-ray spectroscopy. An advantage of NAA is that it is a nondestructive method. However, the requirements of a neutron source and the abundance of ^{10}B restrict its use (Culver et al. 2001; Sah and Brown 1997).

7.2 ENVIRONMENTAL SAMPLES

Methods for the determination of boron in environmental samples are summarized in Table 7-2.

Boron is readily measured in multielement analyses of air, water, and solid waste samples by ICP-AES atomic emission spectroscopy, the method of choice for the determination of boron in modern practice. Although not multielement procedures, colorimetric cucumin and colorimetric carmine methods are still reliable methods for the determination of boron in water, air, and solid waste samples (APHA 1998b; 1998c; EPA 1983). These colorimetric procedures provide adequate methods when ICP instrumentation is not available. Alkali fusion or wet digestion with hydrofluoric acid or a mixture of hydrofluoric acid and other acids are used to digest soils and other geological and silica-rich materials (Sah and Brown 1997).

7.3 ADEQUACY OF THE DATABASE

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

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Collection on filter, hot block/HCl/HNO_3 digestion followed by dilution with water	NIOSH Method 7303 ICP-AES	0.0094 µg/L 0.71 µg/sample	No data	NIOSH 2003
Air (boron carbide)	Collection on filter, ashed, suspended in 2-propanol, redeposited on silver membrane filter	NIOSH Method 7506 X-ray powder diffraction	0.05 mg/ sample	No data	NIOSH 1994
Air (boron trifluoride)	A known volume of air is drawn through a solution of ammonium fluoride; fluoroborate ion is measured using an ion specific electrode	OSHA Method ID216SG Fluoroborate ion specific electrode	10 µg or 0.4 µg/mL of solution	No data	OSHA 1989b
Water	Acidify, inject	APHA Method 3120 ICP-AES	5 µg/L	115.46%[a] 27% RDS[a]	APHA 1998a
Water	Direct analysis	APHA Method 4500-B Colorimetric curcumin	0.2 µg	22.8% RSD	APHA 1998b
Water	Ash, dissolve in acid	APHA Method 4500-B Colorimetric carmine	2 µg	35.5% RSD	APHA 1998c
Water	Direct analysis	EPA Method 212.3 Colori-metric curcumin[b]	0.1–1.0 mg/L (optimal range)	22.8% RSD	EPA 1983
Water	Filter, acidify	EPA Method 200.7 ICP-AES	3 µg/L	115%[a] 27% RSD[a]	EPA 1994
Water, sediments, solid wastes, sludges	Aqueous and solid matrices require acid digestion prior to analysis; pre-filtered, acidified groundwater samples do not need acid digestion	EPA Method 6010C ICP-AES	3.8 µg/L	No data	EPA 2000
Water	Direct analysis	USGS-NWQL Method I-1114 DCP-AES	Applicable range: 10–1,000 µg/L	5.8% RSD	USGS 1989
Aquatic biological material	Nitric acid digestion followed by treatment with 30% hydrogen peroxide	USGS-NWQL Method B-9001-95 ICP-AES	Not calculable	95–96%	USGS 1996a

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water	Acidify to a pH <2.0 with nitric acid	USGS-NWQL Method I-1472-95 ICP-AES	Method reporting limit: 4 µg/L	91.6–109%	USGS 1996b
Water	Filter, acidify	USGS-NWQL Method I-2477-92 ICP-AES	0.5 µg/L	70–103%	USGS 1999
Water	Acidify, filter	USGS-NWQL Method I-4471-97 ICP-OES	13 ug/L	98% (average)	USGS 1998

[a]Percent recovery and relative standard deviation were reported by NEMI (2007).
[b]Same method as APHA (1998b).

APHA = American Public Health Association; DCP = direct current plasma; EPA = U.S. Environmental Protection Agency; ICP-AES = inductively coupled plasma-atomic emission spectroscopy; ICP-OES = inductively coupled plasma-optical emission spectroscopy; NIOSH = National Institute for Occupational Safety and Health; NWQL = National Water Quality Laboratory; OSHA = Occupational Safety and Health Administration; RSD = relative standard deviation; USGS = U.S. Geological Survey

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

7.3.1 Identification of Data Needs

Analytical methods are available and are adequately sensitive to detect boron in biological materials (e.g., blood and urine) and in environmental samples (e.g., water, sediments, and air). No data needs are identified at this time.

Methods for Determining Biomarkers of Exposure and Effect.

Exposure. Boron can be determined sensitively and selectively by ICP-AES and ICP-MS in urine and blood (Goullé et al. 2005; Sah and Brown 1997; Usuda et al. 1998). Analytical methods with satisfactory sensitivity and precision are available to determine levels of boron in human tissues and body fluids.

Effect. Existing methods are sensitive enough to measure background levels for boron in the population and levels at which biological effects occur.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. ICP-AES is a satisfactory multielement method available for the determination of boron in water, air, and solid waste samples (APHA 1998a; EPA 1994; 2000; NIOSH 2003; USGS 1989, 1996a, 1996b, 1999). Colorimetric procedures are as sensitive and precise, but are more labor intensive. Colorimetric procedures do provide adequate methods for those laboratories that do not have ICP instrumentation. There is a need for methods that require less expensive instrumentation, although such methods would be very difficult to develop.

Sampling methodologies for very low level elemental substances like boron continue to pose problems such as nonrepresentative samples, insufficient sample volumes, contamination, and labor-intensive, tedious extraction and purification procedures (Green and Le Pape 1987).

7.3.2 Ongoing Studies

No ongoing studies pertaining to analytical methods for boron were identified in a search of the Federal Research in Progress database (FEDRIP 2007).

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8. REGULATIONS AND ADVISORIES

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

ATSDR has derived an acute-duration inhalation MRL of 0.01 mg boron/m^3 for boron. This MRL is based on a LOAEL of 0.44 mg boron/m^3 for eye, nasal, and throat irritation, cough, and breathlessness in workers (Wegman et al. 1994) and an uncertainty factor of 30 (3 for use of a minimally adverse LOAEL and 10 for human variability).

ATSDR has derived an acute-duration oral MRL of 0.2 mg boron/kg/day for boron. This MRL is based on a NOAEL of 22 mg boron/kg/day associated with a LOAEL of 44 mg boron/kg/day for increased incidence of external, visceral, and cardiovascular malformations and reduced body weight in the fetuses of rabbits administered boric acid via gavage on gestation days 6–19 (Price et al. 1996b) and an uncertainty factor of 100 (10 for interspecies extrapolation and 10 for human variability).

ATSDR has derived an intermediate-duration oral MRL of 0.2 mg boron/kg/day for boron. This MRL is based on a $BMDL_{05}$ of 10.3 mg boron/kg/day estimated from fetal body weight data from two studies in which pregnant rats were exposed to boron in the diet on gestation days 0–20 (Heindel et al. 1992; Price et al. 1996a) and chemical-specific uncertainty factor of 66 (3.3 for toxicokinetic extrapolation from animals to humans, 3.16 for toxicodynamic extrapolation from animals to humans, 2.0 for variability in human toxicokinetics, and 3.16 for variability in human toxicodynamics).

EPA has established an oral reference dose (RfD) of 0.2 mg/kg/day based on decreased fetal weight in a developmental study in Sprague-Dawley rats orally exposed to boric acid from gestation days 0 to 20 (IRIS 2007). EPA has not established an inhalation reference concentration (RfC) for boron and compounds.

Under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), boron oxide, boric acid, borax, and sodium tetraborate are exempt from tolerances for pesticide chemicals in food (EPA 2007e); they are also listed as inerts of unknown toxicity (List 3) in EPA's Categorized List of Inert Pesticide Ingredients (EPA 2004).

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

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	No data	IARC 2006
WHO	Air quality guidelines	No data	WHO 2000
	Drinking water quality guidelines (boron)	0.5 mg/L[a]	WHO 2004
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)		ACGIH 2006
	Borate compounds, inorganic (borax, boric acid, and sodium tetraborate)	2 mg/m^3	
	Boron oxide	10 mg/m^3	
	TLV (ceiling)		
	Boron tribromide	10 mg/m^3	
	Boron trifluoride	3 mg/m^3	
	STEL (15-minute TWA)		
	Borate compounds, inorganic (borax, boric acid, and sodium tetraborate)	6 mg/m^3	
AIHA	Boron trifluoride		AIHA 1999
	ERPG-1[b]	2 mg/m^3	
	ERPG-2[b]	30 mg/m^3	
	ERPG-3[b]	100 mg/m^3	
EPA	AEGL-1[c] (boron trifluoride)		EPA 2007a
	10 minutes	2.5 mg/m^3	
	30 minutes	2.5 mg/m^3	
	60 minutes	2.5 mg/m^3	
	4 hours	2.5 mg/m^3	
	8 hours	2.5 mg/m^3	
	AEGL-2[c] (boron trifluoride)		
	10 minutes	47 mg/m^3	
	30 minutes	47 mg/m^3	
	60 minutes	37 mg/m^3	
	4 hours	24 mg/m^3	
	8 hours	12 mg/m^3	
	AEGL-3[c] (boron trifluoride)		
	10 minutes	140 mg/m^3	
	30 minutes	140 mg/m^3	
	60 minutes	110 mg/m^3	
	4 hours	72 mg/m^3	

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

Agency	Description	Information	Reference
	8 hours	36 mg/m^3	
NATIONAL *(cont.)*			
EPA	Regulated toxic substances and threshold quantities for accidental release prevention pursuant to Section 112(r) of the Clean Air Act		EPA 2007b 40 CFR 68.130
	Boron trichloride	5,000 pounds	
	Boron trifluoride	5,000 pounds	
NIOSH	REL		NIOSH 2005
	Borax (10-hour TWA)	5 mg/m^3	
	Boron oxide (10-hour TWA)	10 mg/m^3	
	Boron tribromide (ceiling)	10 mg/m^3	
	Boron trifluoride (ceiling)	3 mg/m^3	
	Sodium tetraborate (10-hour TWA)	1 mg/m^3	
	IDLH (30-minute exposure)		
	Borax	No data	
	Boron oxide	2,0000 mg/m^3	
	Boron tribromide	No data	
	Boron trifluoride	70 mg/m^3	
	Sodium tetraborate	No data	
OSHA	PEL for general industry		OSHA 2006c 29 CFR 1910.1000
	Boron oxide, total dust (8-hour TWA)	15 mg/m^3	
	Boron trifluoride (ceiling)	3 mg/m^3	
	PEL for shipyard industry		OSHA 2006a 29 CFR 1915.1000
	Boron oxide, total dust (8-hour TWA)	15 mg/m^3	
	Boron tribromide (8-hour TWA)	10 mg/m^3	
	Boron trifluoride (ceiling)	3 mg/m^3	
	PEL for construction industry		OSHA 2006b 29 CFR 1926.55, Appendix A
	Boron oxide, total dust (8-hour TWA)	15 mg/m^3	
	Boron tribromide (8-hour TWA)	10 mg/m^3	
	Boron trifluoride (ceiling)	3 mg/m^3	
	Threshold quantity of highly hazardous chemicals, toxics, and reactives		OSHA 2006d 29 CFR 1910.119
	Boron trichloride	2,500 pounds	
	Boron trifluoride	250 pounds	
b. Water			
EPA	Drinking water contaminant candidate list		EPA 1998 63 FR 10274
	Boron	Yes	

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

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	Drinking water standards and health advisories for boron		EPA 2006
	1-day health advisory for a 10-kg child	4 mg/L	
	10-day health advisory for a 10-kg child	0.9 mg/L	
	DWEL	7 mg/L	
	Lifetime	1 mg/L	
	10^{-4} Cancer risk	No data	
	National primary drinking water standards	No data	EPA 2003
c. Food			
EPA	Inert pesticide ingredients in pesticide products		EPA 2004
	Borax, boric oxide, boric acid, and sodium tetraborate	List 3[d]	
	Tolerances and exemptions from tolerances for pesticide chemicals in food		EPA 2007e 40 CFR 180.101
	Borax, boron oxide, boric acid, and sodium tetraborate	Yes	
FDA	EAFUS		FDA 2007
	Borax, boric acid, and sodium tetraborate	Yes[e]	
	Indirect food additives: adhesives and components of coatings		FDA 2006 21 CFR 175.105
	Borax and boric acid	Yes	
d. Other			
ACGIH	Carcinogenicity classification		ACGIH 2006
	Borate compounds, inorganic (borax, boric acid, and sodium tetraborate)	A4[f]	
EPA	Carcinogenicity classification (boron and boron compounds)	No data[g]	IRIS 2007
	RfC (boron and boron compounds)	Not recommended	
	RfD (boron and boron compounds)	0.2 mg/kg/day	
	Superfund, emergency planning, and community right-to-know; effective date of toxic chemical release reporting		EPA 2007d 40 CFR 372.65
	Boron tribromide, boron trichloride, and boron trifluoride	01/01/95	
	Extremely hazardous substances and their threshold planning quantities		EPA 2007c 40 CFR 355, Appendix A
	Boron trichloride	500 pounds	
	Boron trifluoride	500 pounds	

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

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
NTP	Carcinogenicity classification	No data	NTP 2005

[a]Provisional guideline value because calculated guideline value is below the level that can be achieved through practical treatment methods, source protection, etc.
[b]ERPG-1 is the maximum airborne concentration below which nearly all individuals could be exposed for up to 1 hour without experiencing other than mild, transient health effects; ERPG-2 is the maximum airborne concentration below which nearly all individuals could be exposed for up to 1 hour without experiencing irreversible or other serious adverse effects; and ERPG-3 is the maximum airborne concentration below which nearly all individuals could be exposed for up to 1 hour without life-threatening health effects (AIHA 1999).
[c]AEGL-1 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory effects; AEGL-2 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape; and AEGL-3 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death (EPA 2007e).
[d]List 3: inerts of unknown toxicity
[e]The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.
[f]A4: not classifiable as a human carcinogen
[g]Data are inadequate for an assessment of human carcinogenic potential.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = Acute Exposure Guideline Levels; AIHA = American Industrial Hygiene Association; CFR = Code of Federal Regulations; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; ERPG = Emergency Response Planning Guidelines; FDA = Food and Drug Administration; FR = Federal Register; GRAS = Generally Recognized As Safe; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; STEL = short-term expsoure limit; TLV = threshold limit values; TWA = time-weighted average; WHO = World Health Organization

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10. GLOSSARY

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

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

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

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

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by 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)—The dose expected to result in a specified change of a biological effect (the benchmark response, or BMR), generally 1% to 10% from the untreated population. The BMD is determined by modeling the dose response data in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose, Lower Limit (BMDL)—The lower confidence limit on the benchmark dose. For example, a $BMDL_{10}$ would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%.

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

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

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

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

Carcinogen—A chemical capable of inducing cancer.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Immunological Effects—Functional changes in the immune response.

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

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

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

***In Vivo*—**Occurring within the living organism.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis, 3 being the approximate logarithmic average of 10 and 1 (see for example, Dourson, 1994).

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

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APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

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

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

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

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

are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Environmental Medicine, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Boron and Compounds
CAS Number: 7440-42-8
Date: August 2007
Profile Status: Final Draft Pre-Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 2
Species: Human

Minimal Risk Level: 0.01 [X] mg/m^3 [ ] ppm

Reference: Wegman DH, Eisen EA, Hu X, et al. 1994. Acute and chronic respiratory effects of sodium borate particulate exposures. Envion Health Perspect 102(Suppl 7):119-128.

Experimental design: A population of 106 workers at a borax processing facility was divided into groups of 79 exposed (78 male, 1 female) and 27 comparison (25 male, 2 female) workers. Prior to beginning a work shift, workers were queried as to the presence of a common cold, allergies, asthma, and time of last cigarette smoked. Constant personal air sampling was performed to monitor sodium borate (anhydrous, pentahydrate, decahydrate) levels in each worker's environment, while hourly questionnaires were administered to collect incidences of the following symptoms: nasal, eye, or throat irritation; coughing; or breathlessness. Each reported symptom was given a severity score of 0 (not at all) to 10 (maximal). Incidence rates for each symptom were calculated as the ratio of incidences per number of person-hours at risk (i.e., a work shift length). Results were adjusted for age, smoking, and the presence of common cold using logistic regression modeling of the data.

Effects noted in study and corresponding doses: The comparison group experienced a mean 6-hour TWA total boron exposure of 0.02 mg boron/m^3 as 0.45 mg particulate/m^3 (range ≤1.0 mg particulate/m^3), while the exposed group experienced a mean daily total boron exposure of 0.44 mg boron/m^3 as 5.72 mg particulate/m^3 (range 1–15 mg particulate/m^3). Rate ratios for exposed:comparison groups for symptom incidence ranged from 1.7 for cough to 8.8 for nasal irritation. Symptom incidences of exposed workers in descending order of rate ratios were nasal irritation (9%, rate ratio=8.8), breathlessness (1%, rate ratio=7.1), eye irritation (2%, rate ratio=5.2), throat irritation (3%, rate ratio=2.9), and cough (5%, rate ratio=1.7). All incidence rate ratios were statistically significant ($p<0.001$). The mean severity score for all symptoms in the comparison group was 1.9, with nasal irritation, the most common symptom, having a score of 2.2. In the exposed group, 96% of incidences were given a severity score of ≤4. Given the relatively low average severity of reported symptoms in the exposed group, compared to the unexposed group, respiratory irritation is considered a minimally adverse effect. Regression modeling showed that nasal irritation, the only symptom of exposed workers to be given a severity grade of ≥5, increased in probability from 1% at exposure levels of 1–4 mg particulate/m^3 to 30% at exposure levels of 10–14 mg particulate/m^3.

Dose and end point used for MRL derivation: LOAEL of 0.44 mg/m^3 for nasal, eye, and throat irritation; cough; and breathlessness.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 3 for use of a minimally adverse LOAEL
[ ] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? No.

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

Other additional studies or pertinent information that lend support to this MRL: In an early cross-sectional study of sodium borate workers, past occurrence of symptoms of respiratory irritation such as dryness of the mouth, nose, or throat, dry cough, nose bleeds, and sore throat were reported at elevated frequencies in workers in areas with mean dust concentrations of 8.4 and 14.6 mg particulates/m^3 (1.8 and 3.1 mg boron/m^3, respectively), compared with workers in areas with lower mean dust levels of 4.0 and 1.1 mg particulate/m^3 (0.9 and 0.2 mg boron/m^3) (Garabrant et al. 1984, 1985). In addition, a reduction in forced expiratory volume in 1 second (FEV_1) was measured in a subgroup of smoking workers with estimated high cumulative exposure (≥80 mg particulate/m^3, ≥9 mg boron/m^3) to sodium borate dusts, but not in groups of less-exposed smoking workers or in nonsmoking workers. However, a subsequent survey of FEV_1 in 303 of the original 629 borax workers, 7 years after the original survey, found no exposure-related changes in FEV_1 over this period, when adjustments were made for the effects of age, height, and smoking on FEV_1 (Wegman et al. 1994). Acute-duration laboratory exposures of volunteers to sodium borate dust support the findings of respiratory irritation reported in the occupational studies.

Respiratory irritation was also observed in volunteers exposed to 1.5 mg boron/m^3 (10 mg sodium borate/m^3) for 20 minutes while exercising (Cain et al. 2004). Significantly increased nasal secretions (by mass) and reported significantly higher perception of nasal and throat irritation compared to controls were reported.

Agency Contacts (Chemical Managers): Malcolm Williams, Mike Fay, Moiz Mumtaz

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Boron and Compounds
CAS Number: 7440-42-8
Date: August 2007
Profile Status: Final Draft Pre-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 22
Species: Rabbit

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

Reference: Price CJ, Marr MC, Myers CB, et al. 1996b. The developmental toxicity of boric acid in rabbits. Fundam Appl Toxicol 34:176-187.

The results of this study have also been reported in the following references:

Heindel JJ, Price CJ, Schwetz BA. 1994. The developmental toxicity of boric acid in mice, rats, and rabbits. Environ Health Perspect Suppl 102(7):107-112.

NTP. 1991. Final report on the developmental toxicity of boric acid (CAS No. 10043-35-3) in New Zealand white rabbits. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program. PB92129550.

Experimental design: Groups of 30 pregnant New Zealand white rabbits were given gavage doses of 0, 62.5, 125, or 250 mg boric acid/kg/day (0, 11, 22, or 44 mg boron/kg/day) on gestation days 6–19. Observations were made for clinical signs, maternal and fetal body weight, number of implantations, resorptions, number of live and dead fetuses, and fetal external, visceral, and skeletal defects.

Effects noted in study and corresponding doses: No adverse maternal effects were observed in the 11 or 22 mg boron/kg/day groups. At 44 mg boron/kg/day, decreases in maternal body weight, relative kidney weight, and food consumption were observed. During the treatment period, the rabbits lost 137 g body weight compared to a weight gain of 93 g in controls. No differences in the number of implantation sites per litter were observed; however, there were significant increases in the percent resorptions per litter (6.3, 5.9, 7.7, and 89.9% in the 0, 11, 22, and 44 mg boron/kg/day groups, respectively), percent of litters with one or more resorptions (39, 39, 45, and 95%), and percent of litters with 100% resorption (0, 0, 0, and 73%). The number of live litters was 18, 23, 20, and 6 in the 0, 11, 22, and 44 mg boron/kg/day groups, respectively, and the number of live fetuses was 159, 175, 153, and 14, respectively. A decrease in fetal body weights (92% of controls) was observed at 44 mg boron/kg/day; although the body weight was not significantly different from controls, the effect was considered biologically significant. Significant increases in the percent of fetuses per litter with external (0.8, 1.4, 1.0, and 11.1% in the 0, 11, 22, and 44 mg boron/kg/day groups, respectively), visceral (7.3, 5.9, 7.4, and 80.6%), cardiovascular malformations (2.7, 3.1, 4.2, and 72.2%) and cardiovascular variations (10.6, 5.7, 7.2, and 63.9%) were observed. Although the overall incidence of external malformations was increased at 44 mg boron/kg/day, there were no increases in a specific malformation. The visceral malformations primarily consisted of cardiovascular malformations, particularly interventricular septal defect, enlarged aorta, papillary muscle malformation, and double outlet right ventricle. The cardiovascular variations consisted of abnormal number of cardiac papillary muscles.

Dose and end point used for MRL derivation: NOAEL of 22 mg boron/kg/day as boric acid associated with a LOAEL of 44 mg boron/kg/day as boric acid for developmental effects

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

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

Was a conversion used from ppm in food or water to a mg/body weight dose? No.

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

Other additional studies or pertinent information that lend support to this MRL: A series of studies conducted by Cherrington and Chernoff (2002) also examined the developmental toxicity of boron. A variety of skeletal malformations (including rib agenesis, cervical rib, and fused ribs) were observed in the fetuses of mice receiving two gavage doses of 70 mg boron/kg on gestation day 8 or gestation days 6–8, once daily dose of 88 mg boron/kg/day on gestation days 6–10, or one dose of 131 mg boron/kg on gestation day 8. Multiple thoracic skeletal malformations were observed in the fetuses of mice receiving two doses of 131 mg boron/kg on gestation day 8. Decreases in fetal body weight were also observed in these studies and in studies of mice receiving two gavage doses of 70 mg boron/kg on gestation day 6, 7, 9, or 10.

Developmental effects have also been observed in intermediate-duration studies. Decreases in fetal body weight were observed in rats exposed to 13 or 13.6 mg boron/kg/day on gestation days 0–20 (Heindel et al. 1992; Price et al. 1996a), increases in skeletal abnormalities were observed in rats exposed to 13 mg boron/kg/day on gestation days 0–20 (Price et al. 1996a), and rib cage defects and enlargement of the brain lateral ventricles were observed in rats exposed to 28.4 mg boron/kg/day on gestation days 0–20 (Heindel et al. 1992). In mice exposed to boric acid on gestation days 0–17, reduced fetal body weight and increased skeletal defects were observed at 79 and 175.3 mg boron/kg/day, respectively.

Agency Contacts (Chemical Managers): Malcolm Williams, Mike Fay, Moiz Mumtaz

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Boron and Compounds
CAS Number: 7440-42-8
Date: August 2007
Profile Status: Final Draft Pre-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 60
Species: Rat

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

Reference: Heindel JJ, Price CJ, Field EA, et al. 1992. Developmental toxicity of boric acid in mice and rats. Fundam Appl Toxicol 18:266-277.

Experimental design: Groups of 26–28 pregnant Sprague-Dawley rats and Swiss mice were exposed to 0, 0.1, 0.2, or 0.4% boric acid in the diet on gestation days 0–20. Estimated boron doses are 0, 13.6, 28.5, or 57.7 mg boron/kg/day (0, 78, 163, or 330 mg boric acid/kg/day) for rats and 0, 43, 79, or 176 mg boron/kg/day (0, 248, 452, or 1,003 mg boric acid/kg/day) for mice. Daily observations were made for clinical signs and food and water consumption. At death, body and organ weights were recorded. Maternal kidneys were examined microscopically. Live fetuses were excised, anesthetized, weighed, and examined for skeletal malformations.

Effects noted in study and corresponding doses: Decreased maternal weight gain was observed in the 57.7 mg boron /kg/day group of rats, but not when corrected for gravid uterine weight. Decreased relative kidney and liver weights were seen in the 28.4 mg boron/kg/day group. The incidence and severity of the minimal maternal nephropathy was not dose-related. Mean fetal body weight per litter was significantly reduced (7–15%) in all treated groups. Significant increases in the percentage of malformed fetuses/litter or litter with one or more malformed fetuses was observed at doses ≥28.5 mg boron/kg/day. Noted malformations included anomalies of the eye, central nervous system, cardiovascular system, and axial skeleton. Enlarged lateral ventricles of the brain and agenesis or shortening of the 13th rib were seen in the 57.7 mg boron/kg/day group.

Reference: Price PJ, Strong PL, Marr MC, et al. 1996a. Developmental toxicity NOAEL and postnatal recovery in rats fed boric acid during gestation. Fundam Appl Toxicol 32:179-193.

Experimental design: Groups of 60 female Sprague-Dawley rats were exposed to 0, 0.025, 0.050, 0.075, 0.100, or 0.200% boric acid in the diet on gestation days 0–20. Observations were made for body weight, clinical signs, and food and water consumption. The study was performed in two phases; offspring were evaluated in both phases for post-implantation mortality, body weight, and external, visceral, and skeletal morphology. Phase I was terminated on gestation day 20. The calculated average maternal dose of boron was 0, 3.3, 6.3, 10, 13, or 25 mg boron/kg/day (0, 19, 36, 55, 76, or 143 mg boric acid/kg/day). Phase II dams were allowed to litter and rear their pups until postnatal day (pnd) 21. For these dams, the calculated average doses of boron were 0, 0.2, 6.5, 9.7, 12.9, and 25.3 mg/kg/day (0, 19, 37, 56, 74, and 145 mg boric acid/kg/day). During this phase, the incidence of skeletal defects in control and exposed pups was evaluated at the end of the first 21 postnatal days.

Effects noted in study and corresponding doses: During Phase I of the study, no maternal deaths or clinical signs were associated with boric acid treatment. When corrected for gravid uterine weight,

maternal weight gain was not affected. However, reduced gravid uterine weight resulted in significant trend tests for decreased maternal body weight (gestation days19 and 20) and decreased maternal body weight gain (gestation days 15–18 and 0–20). Dams in the 25 mg boron/kg/day group had a 10% reduction (statistically significant in the trend test, $p<0.05$) in gravid uterine weight compared with controls. Fetal body weights were significantly decreased in the 13 and 25 mg boron/kg/day groups (6 and 12% less than controls) on gestation day 20. Incidences of external or visceral malformations or variations were not treatment-related. However, a significant increase was observed for percentage of fetuses with skeletal malformations (short rib XIII) per litter and variations (wavy rib or wavy rib cartilage) in the 13 and 25 mg boron/kg/day groups. A significant trend test ($p<0.05$) resulted for decrease in rudimentary extra rib on lumbar I (a variation). The LOAEL for Phase I of this study was identified as 13 mg boron/kg/day, based on decreased fetal body weight and skeletal malformations. The NOAEL for this phase was identified as 10 mg boron/kg/day.

In the Phase II study, a significant trend for increased number and percent of dead pups was seen between pnd 0 and 4, but not between pnd 4 and 21. This appeared to be due to the non-significant early postnatal mortality in the 25.3 mg boron/kg/day group. There were no effects of boric acid on the pup body weight from pnd 0 to 21; therefore, fetal body weight deficits (identified in Phase I) did not continue into the postnatal period (Phase II). The percentage of pups per litter with short rib XIII was increased on pnd 21 in the 25.3 mg boron/kg/day group. A LOAEL of 25.3 mg boron/kg/day, with an associated NOAEL of 12.9 mg boron/kg/day, was identified for skeletal malformations in Phase II of this study.

Dose and end point used for MRL derivation: $BMDL_{05}$ of 10.3 mg/kg/day for reduced fetal body weight

[ ] NOAEL [ ] LOAEL [X] $BMDL_{05}$

Allen et al. (1996) performed multiple benchmark dose (BMD) analyses on single-study or combined data from Heindel et al. (1992) and Price et al. (1996a) for all statistically significant developmental end points (Table A-1). Fetal body weight changes were analyzed using the average fetal weight for each litter with live fetuses. The modeling of rib effects aimed to differentiate whether treatment-related differences in the lumbar rib were variations or malformations. Thus, a weighting scheme was applied to represent three possible interpretations of severity of this effect; that is, a missing rib is: (a) trivially different from "normal" (1/6 weighting), (b) intermediate between a trivial or frank malformation (1/2 weighting), or (c) considered a frank malformation (5/6 weighting). Rib count analysis involved adjusting up (if rudimentary or full lumbar ribs present) or down (shortened rib XIII or rib agenesis) the base count of 13 rib pairs for each fetus analyzed. Benchmark responses (BMRs) were chosen for each end point. The BMD expected to result in the BMR, while the $BMDL_{05}$ was defined as the 95% lower bound on the BMD. The data were modeled with a continuous power model using an F-test evaluation of goodness of fit.

Table A-1. Benchmark Dose Modeling of Developmental Effects of Oral Boric Acid Exposure to Rats

End point	Study data	Goodness-of-fit p-value[a]	BMD[b] (mg boron/ kg/day)	Lower bound on BMD[c] (mg boron/ kg/day)
Fetal body weight as continuous data (BMR=5% reduction)	Heindel et al. 1994	0.24	14.0	9.8
	Price et al. 1996a	0.89	11.9	8.2
	Combined	0.58	13.7	10.3
Fetal body weight as continuous data (BMR=1/2 standard deviation below control)	Heindel et al. 1994	0.24	12.8	8.4
	Price et al. 1996a	0.89	8.6	5.4
	Combined	0.58	11.4	8.4
Fetal body weight as dichotomous incidence data (BMR=5% reduction)	Heindel et al. 1994	0.44	22.6	20.1
	Price et al. 1996a	0.01	8.2	5.4
	Combined	NA	NA	NA
Shortening or agenesis of rib XIII	Heindel et al. 1994	0.07	24.9	18.6
	Price et al. 1996a	0.64	29.9	21.5
	Combined	0.42	24.5	21.0
Missing lumbar ribs	Heindel et al. 1994	0.99	1.2	0.3
	Price et al. 1996a	0.78	1.5	0.6
	Combined	0.99	2.1	0.9
Rib effects analysis: 1/6 weighting for absence of lumbar rib	Heindel et al. 1994	0.27	21.2	16.5
	Price et al. 1996a	0.78	32.9	25.7
	Combined	NA	NA	NA
Rib effects analysis: 1/2 weighting for absence of lumbar rib	Heindel et al. 1994	0.02	13.5	10.2
	Price et al. 1996a	0.64	45.3	30.3
	Combined	NA	NA	NA
Rib effects analysis: 5/6 weighting for absence of lumbar rib	Heindel et al. 1994	<0.001	24.9	20.5
	Price et al. 1996a	0.53	53.7	31.2
	Combined	NA	NA	NA
Rib effects analysis: rib count for absence of lumbar rib	Heindel et al. 1994	0.002	16.5	12.8
	Price et al. 1996a	0.08	25.6	16.5
	Combined	NA	NA	NA

[a]p-values for assessing adequacy of the models for predicting the observed data of Heindel et al. (1992) and Price et al. (1996a)
[b]Benchmark dose: model estimated dose expected to result in the BMR
[c]95% lower bound on the BMD

BMR = benchmark response; NA = not applicable

Source: Heindel et al. 1992; Price et al. 1996a

A likelihood ratio test indicated that the response data from both studies could be modeled as a single dose-response function. Of the developmental end points modeled, the lowest resulting $BMDL_{05}$ was 10.3 mg boron/kg/day for fetal body weight (litter weight averages), which was similar to the NOAEL of 10 mg boron/kg/day from the Price et al. (1996a) study.

Uncertainty Factors used in MRL derivation: A total uncertainty factor of 66 was used.

[ ] 10 for use of a LOAEL
[X] 3.3 for extrapolation of toxicokinetics from animals to humans
[X] 3.16 for extrapolation of toxicodynamics from animals to humans
[X] 2.0 for human toxicokinetic variability
[X] 3.16 for human toxicodynamic variability

In deriving a reference dose (RfD) for chronic oral exposures to boron, the U.S. EPA applied chemical-specific uncertainty factors to the $BMDL_{05}$ of 10.3 mg boron/kg/day reported by Allen et al. (1996) (EPA 2004). Rather than using the default uncertainty factors of 10 for interspecies extrapolation and 10 for interindividual human variability, each uncertainty factor was further delineated into toxicokinetic and toxicodynamic components specific to boron. Since the critical effect (reduced fetal body weight in animals) and point of departure ($BMDL_{05}$ of 10.3 mg/kg/day) for intermediate oral exposure to boron are the same as those for chronic oral exposures, as identified by EPA (2004), the chemical-specific uncertainty factors derived by U.S. EPA to derive a chronic RfD are appropriate for use in deriving the intermediate-duration MRL.

Briefly, each uncertainty factor of 10 for extrapolation from animals to humans and human variability was initially separated into default toxicokinetic and toxicodynamic adjustment factors of 3.16 ($10^{0.5}$) each to account for species differences in toxicokinetic disposition and toxicodymanic responses to orally-ingested boron. The same division was made for the uncertainty factor of 10 for human variability. Thus, the composite uncertainty factor (UF_{TOTAL}) for the intermediate-duration oral MRL is defined as given by EPA (2004) as:

$$UF_{TOTAL} = (AF_{AK} \times AF_{AD} \times AF_{HK} \times AF_{HD} \times UF)$$

where:

AF_{AK} = interspecies toxicokinetic adjustment factor
AF_{AD} = interspecies toxicodynamic adjustment factor
AF_{HK} = interindividual toxicokinetic adjustment factor
AF_{HD} = interindividual toxicodynamic adjustment factor
UF = other uncertainty factors (e.g., use of a LOAEL instead of a NOAEL)

Since no data were available to adequately describe the mode(s) or mechanism(s) of action for boron toxicity in animals or humans, the default toxicodynamic adjustment factor of 3.16 was used to account for inter- and intraspecies uncertainties in toxicodynamics.

The pregnant female is considered to be a sensitive population for boron exposure, as fetal effects in rats are the most sensitive end point identified for boron toxicity. Since boron exhibits near first-order toxicokinetics, distributing freely between total body water and tissues (except for bone, in which it accumulates to approximately 4-fold that of plasma [Chapin et al. 1997]), variability between maternal and fetal kinetics should be essentially equal. Thus, maternal boron plasma concentration is an appropriate surrogate for fetal plasma levels. No data are available to relate rat and human plasma boron concentration. However, boron is not metabolized, but almost completely eliminated in the urine, making renal clearance an appropriate kinetic factor for comparison of toxicokinetic differences between rats and humans. Given the known distribution of boron to total body water and bone, two-compartment

pharmacokinetic models for boron in rats and humans can describe plasma concentration in terms of renal clearance. Boron's toxicity is likely to be related to a continuous exposure over an extended portion of fetal development in which a steady state of circulating boron is achieved. Under the assumption of steady-state plasma boron levels, and assuming approximately complete clearance of born to urine, the two-compartment model can be simplified to the following expression:

$$C_{SS} = (D_e \times f_a \times BW) / Cl$$

where:

D_e = external dose of ingested boron (mg boron/kg body weight/day)
f_a = fraction of ingested boron absorbed from the gut
BW = body weight (kg)
Cl = renal clearance (mL/minute)

Assuming that the ratio of 1 for internal, steady-state doses in rats and humans results in equivalent responses, the expressions for the plasma boron concentration in rats and humans can be expressed as the following ratio, which serves as the AF_{AK}:

$$AF_{AK} = (Cl_R \times f_{AH} \times BW_H) / (Cl_H \times f_{AR} \times BW_R)$$

where the subscripts R and H represent rats and humans. Values for mean renal clearance of 1.0 and 66.1 mL/minute in pregnant rats and humans, respectively, were derived from the studies of Vaziri et al. (2001), and Pahl et al. (2001), which also provided pregnant rat and human body weights of 0.303 and 67.6 kg, respectively. Using gastrointestinal absorption fractions of 0.92 (Schou et al. 1984) and 0.95 (Vanderpool et al. 1994) for f_{AH} and f_{AR}, respectively, AF_{AK} is derived as follows:

$$AF_{AK} = (1.00 \times 0.92 \times 67.6) / (66.1 \times 0.95 \times 0.303)$$
$$= 62.2 / 19.0$$
$$= 3.3$$

The assessment of human variability in boron toxicokinetics utilized glomerular filtration rate (GFR) as a surrogate for renal clearance. Pregnant women were considered the sensitive population, particularly those women with compromised renal function (3–5% preeclamptic women in the U.S. population). Using a modification of Dourson et al. (1998), data from women with normal renal function were used to define an AF_{HK} as:

$$AF_{HK} = GFR_{AVG} / (GFR_{AVG} - (3 \times SD_{GFR}))$$

where GFR_{AVG} and SD_{GFR} are mean and standard deviation of the GFR for healthy women. Three standard deviations below the mean GFR was chosen to account for the women with very low GFR. From the studies of Dunlop (1981), Krutzen et al. (1992), and Sturgiss et al. (1996), a mean GFR of 161.5 mL/minute and a mean GFR-$3SD_{GFR}$ of 85.8 mL/minute resulted in an AF_{HK} of 1.93. This number was rounded to 2.0 to account for uncertainties in human GFR.

Based on these analyses, the total uncertainty factor applied to the $BMDL_{05}$ of 10.3 mg boron/kg is derived as:

$$UF_{TOTAL} = (AF_{AK} \times AF_{AD} \times AF_{HK} \times AF_{HD} \times UF)$$
$$= (3.3 \times 3.16 \times 2.0 \times 3.16 \times 1)$$
$$= 66$$

Was a conversion used from ppm in food or water to a mg/body weight dose? No.

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

Other additional studies or pertinent information that lend support to this MRL: Reproductive effects, including testicular atrophy and histopathology, sperm abnormalities, and reduced sperm production have been observed in mice, rats, and dogs after intermediate-duration ingestion of doses of 26 mg boron/kg/day (as boric acid or borax) and higher (Dixon et al. 1979; Fukuda et al. 2000; Harris et al. 1992; Ku et al. 1993a; Kudo et al. 2000; Seal and Weeth 1980; Treinen and Chapin 1991; Weir and Fisher 1972; Yoshizaki et al. 1999). Systemic effects have been observed in rats and dogs at higher doses. Hematological alterations (splenic extramedullary hematopoiesis and decreased hemoglobin levels) have been observed at 60.5 or 72 mg boron/kg/day (NTP 1987; Weir and Fisher 1972), desquamation of skin on paws and tail and inflamed eyes have been observed in rats exposed to 150 mg boron/kg/day (Weir and Fisher 1972), and hyperkeratosis and/or acanthosis of the stomach has been observed at 577 mg boron/kg/day (NTP 1987).

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APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

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

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

Chapter 2

Relevance to Public Health

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

1. What effects are known to occur in humans?

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

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

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

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

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

Interpretation of Minimal Risk Levels

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

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

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

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

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

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

LEGEND

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

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

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

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

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

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

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

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

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

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

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

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

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

LEGEND

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

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

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

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

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

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

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

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

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

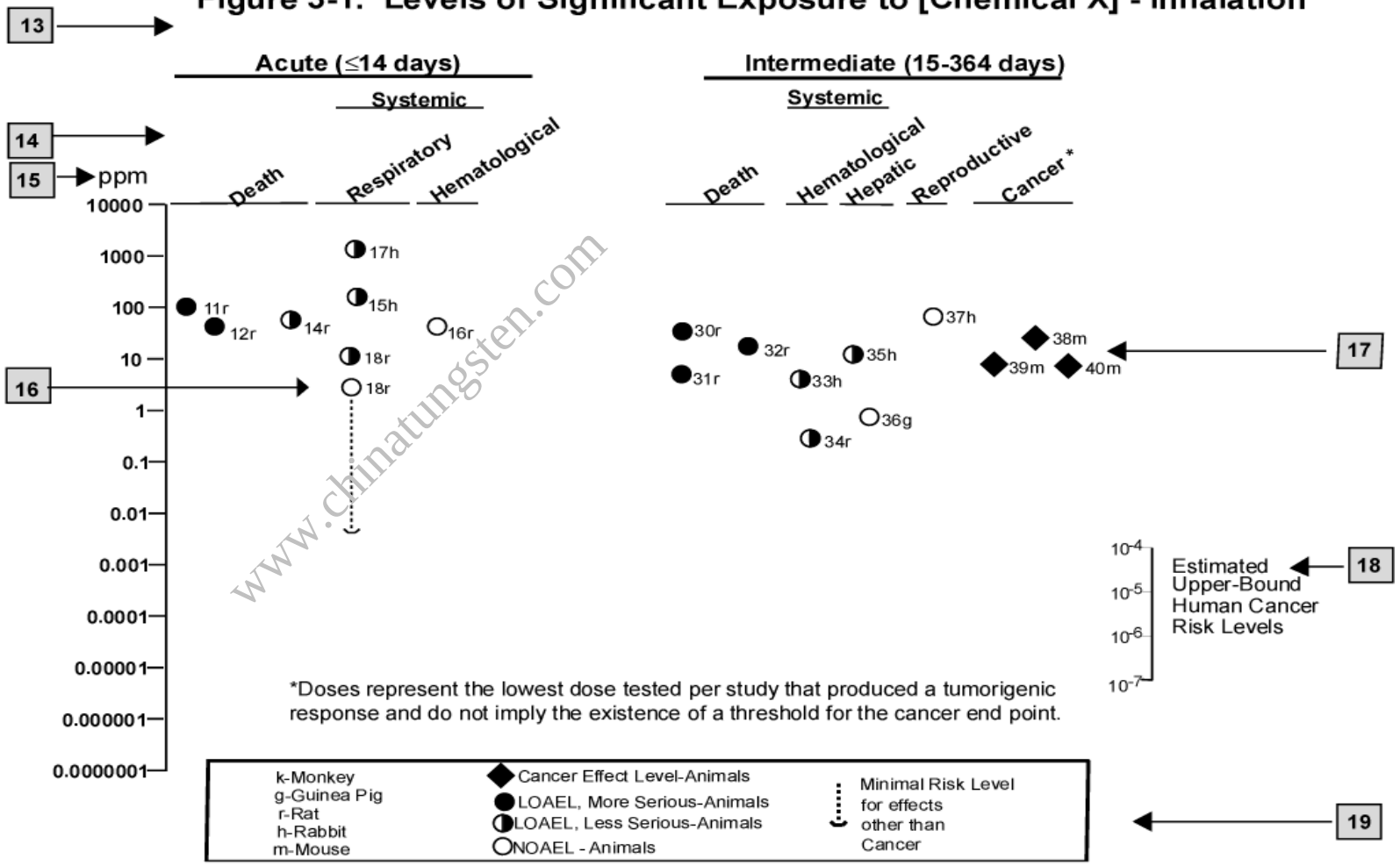
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

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

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

SAMPLE

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



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

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

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

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

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

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

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APPENDIX D. INDEX