TOXICOLOGICAL PROFILE FOR
BORON AND COMPOUNDS

Agency for Toxic Substances and Disease Registry
U.S. Public Health Service

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DISCLAIMER

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

FOREWORD

The Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) extended and amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances which are most commonly found at facilities on the CERCLA National Priorities List and which pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The lists of the 250 most significant hazardous substances were published in the Federal Reeister on April 17, 1987; on October 20, 1988; on October 26, 1989; and on October 17, 1990. A revised list of 275 substances was published on October 17, 1991.

Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the lists. Each profile must include the following content:

(A) An examination, summary, and interpretation of available toxicological information and epidemiological evaluations on the hazardous substance in order 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 which present a significant risk to human health of acute, subacute, and chronic health effects.

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

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The original guidelines were published in the Federal Register on April 17, 1987. Each profile will be revised and republished as necessary,

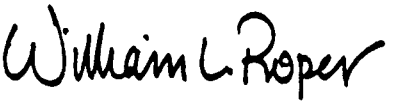
The ATSDR toxicological profile is intended to characterize succinctly the toxicological and adverse health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature (that has been peer-reviewed) that describes a hazardous substance's toxicological properties, Other pertinent literature is also presented but 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.

Foreword

Each toxicological profile begins with a public health statement, which 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 will be identified by ATSDR, the National Toxicology Program (NTP) of the Public Health Service, and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the beginning of the document.

The principal audiences for the toxicological profiles are health professionals at the federal, state, and local levels, interested private sector organizations and groups, and members of the public.

This profile reflects our assessment of all relevant toxicological testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, the Centers for Disease Control, the NTP, and other federal agencies. It has also been reviewed by a panel of nongovernment peer reviewers. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.



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1. PUBLIC HEALTH STATEMENT

This Statement was prepared *to* give you information about boron and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1,177 sites on its National Priorities List (NPL). Boron has been found in at least 21 of these sites. However, we do not know how many of the 1,177 NPL sites have been evaluated for boron. As EPA evaluates more sites, the number of sites at which boron is found may change. This information is important for you to know because boron may cause harmful health effects and because these sites are potential or actual sources of human exposure to boron.

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

If you are exposed to a hazardous chemical such as boron, several factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such as age, sex, nutritional status, family traits, life style, and state of health.

1.1 WHAT IS BORON?

Boron is a solid substance that widely occurs in nature. It usuallydoes not occur alone, but is often found in the environment combined with other substances to form compounds called borates. Common borate compounds include boric acid, salts of borates, and boron oxide. Boron and salts of borate have been found at hazardous waste sites. Boron alone does not dissolve in water nor does it evaporate easily, but it does stick to soil particles. No information was found on whether common forms of boron evaporate easily or stick to soil particles; however, these forms do dissolve in water.

Boron is present in air, water, and soil, but no information is available on how long it remains in these media. There is also no information available on the occurrence of borates in the environment or on how long they persist in the environment.

Borates are used mostly in the production of glass. They are also used in fire retardants, leather tanning and finishing industries, cosmetics, photographic materials, with certain metals, and for high-energy fuel. Pesticides for cockroach control and wood preservatives also contain borates.

1. PUBLIC HEALTH STATEMENT

More information on the properties and uses of boron and boron compounds and how they behave in the environment may be found in Chapters 3, 4, and 5.

1.2 HOW MIGHT I BE EXPOSED TO BORON?

Boron occurs mainly in the environment through release into air, water,or soil after natural weathering processes. It can also be released from glass manufacturing, coal-burning power plants, copper smelters, and through its use in agricultural fertilizer and pesticides. It is estimated that releases from these sources are less than through natural weathering processes.

You can be exposed to boron in food (mainly vegetables and fruits),water, air, and consumer products. Infants, in particular, can be exposed to borates in products used to control cockroaches. Since boron is taken up from the soil by plants, it can enter the food chain. Although boron has been found in animal tissue, it does not accumulate and it is not likely that eating fish or meat will increase the boron levels in your body. Boron has been found in groundwater at very low levels. Background levels of boron up to 5 parts of boron in 1 million parts (ppm) of surface water have been reported. However, in dry areas where there are natural boron-rich deposits, boron concentrations can be as high as 360 ppm. No data were found on the occurrence of boron compounds in surface or groundwater. While current drinking water surveys do not report any levels of boron, it has been found in tap water in the past. Levels reported in drinking water were less than l-3 ppm. There is potential for exposure to boron through contact with soil, since boron sticks to soil particles. Background levels up to 300 ppm have been reported. Exposure to air contaminated with boron is not likely to occur in the general population; however, there is risk of exposure to borate dust in the workplace. Concentrations from 1-14 milligrams of boron dust per cubic meter of air (mg/m^3) have been reported in borax mining and refining plants and at sites where boric acid is manufactured. Exposure to boron may also occur from the use of consumer products, including cosmetics, topical medical preparations, and some laundry products. The average daily boron intake has been estimated to be 10-25 mg.

Further information on how you might be exposed to boron is given in Chapter 5.

1.3 HOW CAN BORON ENTER AND LEAVE MY BODY?

Boron can enter your body when you eat food (fruit and vegetables) breathe borate dust in the air, and when damaged skin comes in contact with it. Because very small amounts of boron are present in all drinking water, boron can enter your body when you drink water. When boron enters the body by mouth or when you breathe borate dust, it goes to the intestines where it is passed to various parts of the body including the liver, brain, and kidney. No information is available on what factors affect how fast boron enters the body. However, animal studies suggest boron readily enters the body after contact with damaged skin. Most of the boron leaves the body in urine

primarily from food eaten. Over half of the boron taken by mouth can be found in urine within 24 hours and the other half can be detected for up to 4 days. Boron compounds can be found in urine up to 23 days if you are accidentally exposed to very large amounts.

Further information on how boron enters and leaves the body is given in Chapter 2.

1.4 HOW CAN BORON AFFECT MY HEALTH?

If humans eat large amounts of boron (4,161 ppm) over short periods of time, it can affect the stomach, intestines, liver, kidney, and brain and can eventually lead to death. Irritation of the nose and throat or eyes can occur if small amounts of boron (4.1 mg/m^3) are breathed in. Boron can irritate the eyes if it comes in contact with them for long periods of time. Animal studies indicate that the male reproductive organs, especially the testes, are affected if large amounts of boron are eaten or drunk for short or long periods of time. Studies in animals also indicate delayed development and structural defects in offspring, primarily in the rib cage, from maternal exposure to boron during pregnancy. These effects have not been seen in humans. Irritation of the nose can occur in animals if large amounts of boron are breathed in for long periods of time. These effects have not been seen in humans. No information is available on whether boron is likely to cause cancer in humans. There is no evidence of cancer in animals exposed to boron for long periods of time.

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

1.5 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO BORON?

There are reliable and accurate ways of measuring boron in the body. Blood and urine can be examined to determine if excessive exposure to boron has occurred. Boron and, to a limited extent, boron-related compounds can be measured in body fluids. However, special equipment is needed for detection and analysis. Tests are not routinely available in a doctor's office. It is not known whether boron levels measured in the body can be used to predict potential health effects.

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

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

The federal government has set regulatory standards and guidelines to protect individuals from the effects that may occur if exposed to boron. The EPA has established tolerances for total boron of 30 ppm in or on cottonseed and 8 ppm in or on citrus fruits. The Food and Drug Administration has

designated that borax and boric acid are generally recognized as safe (GRAS) as indirect food additives in adhesive components, components of paper, paperboard, sizing and coatings. The Occupational Safety and Health Administration (OSHA) has set a permissible exposure limit of 10 mg/m^3 for boron oxide and sodium tetraborate in the workplace air for 8 hour/day exposures over a 40-hour work week. Limits of 10 mg)m^3 for boron tribromide and 3 mg/m^3 for boron trifluoride have been set.

Additional information on governmental regulations regarding boron can be found in Chapter 7.

1.7 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns not covered here, please contact your state health or environmental department or:

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

This agency can also provide you with information on the location of the nearest occupational and environmental health clinic. Such clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of boron and compounds and a depiction of significant exposure levels associated with various adverse health effects. It contains descriptions and evaluations of studies and presents levels of significant exposure for boron based on toxicologicalstudies and epidemiological investigations.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals 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, developmental, reproductive, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods--acute (less than 15 days), 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. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear. They should also help to determine 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 tables and figures may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposureassociated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAEL) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels, MRLs) may be of interest to health professionals and citizens alike.

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer effect for each exposure duration. MRLs include adjustments to reflect human variability from laboratory animal data to humans.

Although methods have been established to derive these levels (Barnes et al. 1988; EPA 1989a), 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.

2.2.1 Inhalation Exposure

2.2.1.1 Death

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

2.2.1.2 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/ocular effects after acute inhalation exposure in humans or animals for any duration category.

Information on respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, 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 2-l and plotted in Figure 2-1.

Respiratory Effects. Boron (as boron oxide and boric acid dusts) has been shown to cause irritation of the upper respiratory tract in humans. Based on a medical questionnaire from 113 workers (96% males, 4% females) employed in the borax industry for an average of 11 years, mean exposures of 4.1 mg/m^3 to boron oxide and boric acid dusts were associated with dryness of the mouth, nose, or throat, sore throat, and productive cough (Garabrant et al. 1984). While the authors reported differences between the test and control groups in age and numbers of smokers, no differences in symptoms were observed. Similarly, symptoms of acute respiratory irritation were related to exposures to borax dust at concentrations of 4 mg/m^3 or more in a crosssectional study of 629 borax workers actively employed for 11.4 years (Garabrant et al. 1985). Decreases in the forced expiratory volume (FEV_1) were seen among smokers who had cumulative borax exposures of 80 mg/m^3 or greater but were not seen among less exposed smokers or among nonsmokers. Radiographic abnormalities were not found. It was determined in a follow-up of the Garabrant et al. 1985 study that the cumulative borax exposure effect

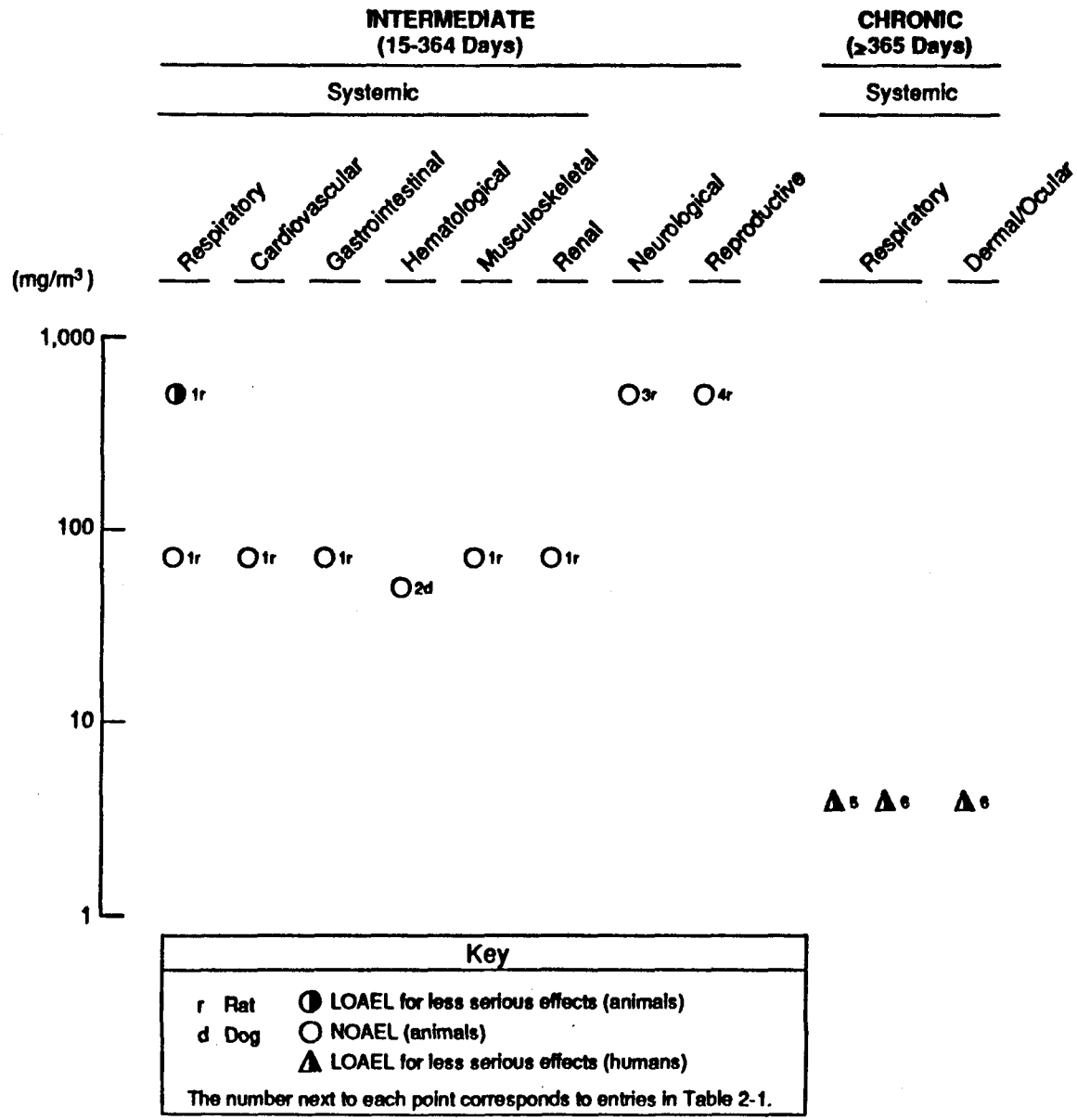
TABLE 2-1. Levels of Significant Exposure to Boron and Compounds - Inhalation

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (mg/m^3)	LOAEL (effect) Less serious (mg/m^3)	LOAEL (effect) Serious (mg/m^3)	Reference	Form
INTERMEDIATE EXPOSURE								
Systemic								
1	Rat	6-24 wk 5d/wk 6hr/d	Resp	77	470 (respirtory irritation)		Wilding et al. 1959	BO
			Cardio	77				
			Musc/skel	77				
			Renal	77				
			Gastro	77				
2	Dog	23 wk	Hemato	57			Wilding et al. 1959	BO
Neurological								
3	Rat	6-24 wk 5d/wk 6hr/d		470			Wilding et al. 1959	BO
Reproductive								
4	Rat	6-24 wk 5d/wk 6hr/d		470			Wilding et al. 1959	BO
CHRONIC EXPOSURE								
Systemic								
5	Human	11.4 yr (mean)	Resp		4.1 (respiratory irritation)		Garabrant et al. 1985	BX
6	Human	11.4 yr (mean)	Resp		4.1 (respiratory irritation)		Garabrant et al. 1984	BX, BA, BO
			Derm/oc		4.1 (eye irritation)			

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

BA = boric acid; BO = boron oxide; BX = borax; Cardio = cardiovascular; d = day(s); Derm/oc = dermal/ocular; Gastro = gastrointestinal; Hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s); yr = year(s)

FIGURE 2-1. Levels of Significant Exposure to Boron and Compounds – Inhalation



found previously was probably due to smoking workers with longer boron work histories and who smoke disproportionately more than those with shorter work histories. There was no indication that borax exposure at the levels studied (up to 15 mg/m^3) impaired pulmonary function (Wegman et al. 1991). Direct irritation to mucous membranes of the nose and throat was also studied by Wegman et al. (1991) using an irritation scoring system together with realtime measurements of borax exposure concentrations. The study concluded that borates 'are mild irritants. However, these effects are likely to occur at concentrations exceeding 10 mg/m^3 (OSHA Permissible Exposure Limit).

Animal studies suggest that the respiratory tract is susceptible to boron toxicity. Rats exposed to 470 mg/m^3 boron oxide aerosol for 10 weeks developed reddish exudates from their noses, but there were no deaths or signs of lung damage (Wilding et al. 1959). No changes were observed in rats in the 77 mg/m^3 dose group after 24 weeks of exposure, or in dogs exposed to a concentration of 57 mg/m^3 for 23 weeks (Wilding et al. 1959).

Cardiovascular Effects. Animal data are sparse. Rats exposed to aerosols of boron oxide at a concentration of 77 mg/m^3 for 6 weeks showed no histopathological effects in the cardiovascular system (Wilding et al. 1959).

Gastrointestinal Effects. Animal data are sparse. No changes were seen in the gastrointestinal tract of rats exposed to aerosols of boron oxide at a concentration of 77 mg/m^3 for 6 weeks (Wilding et al. 1959).

Hematological Effects. Little is known concerning the effects of boron in animals. Rats exposed to aerosols of boron oxide for lo-24 weeks (up to 470 mg/m^3) and dogs for 23 weeks (57 mg/m^3) showed no significant changes in total red and white blood cell count, hemoglobin, hematocrit, and differential count (Wilding et al. 1959).

Musculoskeletal Effects. Animal data are sparse. No histopathological effects of exposure were observed in the femur, rib, and muscle of rats exposed to aerosols of boron oxide at a concentration of 77 mg/m^3 for 6 weeks (Wilding et al. 1959).

Renal Effects. Data on the effects of boron in animals are sparse. No renal effects were observed in rats exposed to aerosols of boron oxide at a concentration of 77 mg/m^3 for 6 weeks (Wilding et al. 1959).

Dermal/Ocular Effects. Human occupational exposure to a mean concentration of 4.1 mg/m^3 (as boron oxide and boric acid dust) produced eye irritation following chronic exposures in workers employed for an average of 11 years (Garabrant et al. 1984, 1985).

2.2.1.3 Immunological Effects

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

2.2.1.4 Neurological Effects

No studies were located regarding neurological effects in humans after inhalation exposure to boron. Adverse effects were not found on the brain of rats exposed to aerosols of boron oxide at a concentration of 77 mg/m^3 for 6 weeks (Wilding et al. 1959).

2.2.1.5 Developmental Effects

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

2.2.1.6 Reproductive Effects

Limited data were located regarding reproductive effects in humans after inhalation exposure to boron. One study was reported involving occupational exposure (10 years or greater) to boron aerosols (22-80 mg/m^3) in males engaged in the production of boric acids (Tarasenko et al. 1972). The study group was small, consisting of 28 men. Low sperm counts, reduced sperm motility and elevated fructose content of seminal fluids were observed.

In animals, no effects were found on the ovary or testes of rats exposed to aerosols of boron oxide at a concentration of 77 mg/m^3 for 6 weeks (Wilding et al. 1959).

2.2.1.7 Genotoxic Effects

No studies were located regarding the genotoxic effects in humans or animals after inhalation exposure to boron. Genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

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

2.2.2 Oral Exposure

2.2.2.1 Death

Studies in humans, particularly infants, show that boron (as boric acid) can be lethal following ingestion. Infants who ingested formula accidentally prepared with 2.5% aqueous solution of boric acid died within 3 days after exposure (Wong et al. 1964). It was estimated that the amount of boric acid consumed ranged from 4.51 to 14 g. Although 5 of 11 infants died, the authors provided histopathological data and weights for only 2 infants who had ingested 9.25 g (505 mg boron/kg/day) and 14 g (765 mg boron/kg/day) (Wong et al. 1964). Infants became lethargic and developed vomiting and diarrhea.

Degenerative changes were seen in the liver, kidney, and brain. Acute exposure to dose levels of 895 mg boron/kg as boric acid was not lethal in one adult (Linden et al. 1986).

In animals, boron (as boric acid and borax) is lethal following acute, intermediate, and chronic oral exposures. Estimates of oral LD,, in rats were 898 and 642 mg boron/kg (as boric acid and borax, respectively) (Smyth et al. 1969) and 510 and 550 mg boron/kg as borax and boric acid (Weir and Fisher 1972). No deaths were reported in dogs exposed to 696 mg boron/kg as boric acid and 738 mg boron/kg as borax (Weir and Fisher 1972). In a 14-day repeated-dose feeding study in male mice, doses of 2,251 and 3,671 mg boron/kg/day (as boric acid) were lethal in 20% and 60% of males, respectively (NTP 1987). The mice were lethargic and the spleen, liver, and renal medullae were discolored. Hyperplasia and dysplasia of the forestomach were also observed (NTP 1987).

Survival was also reduced in mice following intermediate-duration exposure. Males (10%) died after exposure to a dose of 288 mg boron/kg/day (as boric acid) in the diet, while 80% of males and 60% of females died at 577 mg boron/kg/day (NTP 1987). Hyperkeratosis and/or acanthosis in the stomach and extramedullary hematopoiesis of the spleen in both sexes were observed at the highest dose tested (577 mg boron/kg/day). There was 100% mortality in rats fed 263 mg boron/kg/day for 90 days (Weir and Fisher 1972). Congestion of liver and kidneys, small gonads, and brain swelling were reported. When male mice consumed 48 and 96 mg boron/kg/day (as boric acid) for 103 weeks, mortality *was* 40% and 56%, respectively, compared to 18% in untreated controls (NTP 1987). No clinical signs were reported; however, boron caused increased incidence of testicular atrophy and interstitial hyperplasia. Mortality in female mice was 30% and 24% (48 and 96 mg boron/kg/day) compared to 34% in the untreated controls (NTP 1987).

The LD_{50} values and the highest NOAEL values in animals and the lowest level at which death was reported in humans and the duration categories are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.2 Systemic Effects

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

Information on respiratory, gastrointestinal, hematological, 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 2-2 and plotted in Figure 2-2.

Respiratory Effects. Widespread vascular congestion and hemorrhages in the lungs were reported in one infant who ingested 505 mg boron/kg/day (Wong et al. 1964).

TABLE 2-2. Levels of Significant Exposure to Boron and Compounds - Oral

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Form
ACUTE EXPOSURE									
Death									
1	Human	(F)	3-5 d				505 (increased mortality)	Wong et al. 1964	BA
2	Rat	(F)	1 d				550 (LD50)	Weir and Fisher 1972	BA
3	Rat	(W)	1 d				642 (LD50)	Smyth et al. 1969	BX
4	Rat	(F)	1 d				510 (LD50)	Weir and Fisher 1972	BX
5	Rat	(W)	1 d				898 (LD50)	Smyth et al. 1969	BA
6	Mouse	(F)	14 d				2251 (increased mortality)	NTP 1987	BA
7	Dog	(C)	1 d		738			Weir and Fisher 1972	BX
8	Dog	(C)	1 d		696			Weir and Fisher 1972	BA
Systemic									
9	Human	(F)	3-5 d	Resp			505 (vascular congestion, hemorrhage in infants)	Wong et al. 1964	BA
				Hepatic			505 (parenchymatous degeneration, jaundice, fatty changes, congestion in infants)		
				Renal			765 (parenchymatous degeneration, reduced urine output, protein in urine in infants)		
				Derm/oc		505 (extensive shedding of skin)			

TABLE 2-2 (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Form
10	Human	(F)	3-5 d	Gastro		184 (vomiting, diarrhea in infants)		Wong et al. 1964	BA
				Derm/oc		505 (erythema, desquamation in infants)			
11	Human	(F)	1 d	Gastro		241 (vomiting, diarrhea)		Linden et al. 1986	BA
12	Mouse	(F)	14 d	Gastro		2251 (gastric hyperplasia and dysplasia)		NTP 1987	BA
Neurological									
13	Human	(F)	3-5 d				505 (perivascular hemorrhage, congestion, thrombosis, edema in infants)	Wong et al. 1964	BA
INTERMEDIATE EXPOSURE									
Death									
14	Rat	(F)	90 d				263 (100% mortality)	Weir and Fisher 1972	BX
15	Rat	(F)	90 d				263 (100% mortality)	Weir and Fisher 1972	BA
16	Mouse	(F)	13 wk				144 (increased mortality)	NTP 1987	BA
Systemic									
17	Rat	(F)	90 d	Other	88			Weir and Fisher 1972	BX
18	Rat	(W)	3-14 wk	Hepatic	20.8			Settimi et al. 1982	BX
19	Rat	(W)	70 d	Other		23.7 (decreased body and spleen weights)		Seal and Weeth 1980	BX

TABLE 2-2 (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Form
20	Rat	(F)	90 d	Other		88 (decreased body weight)		Weir and Fisher 1972	BA
21	Dog	(F)	90 d	Other	44			Weir and Fisher 1972	BA
22	Dog	(F)	90 d	Hemato	4.4	44 (decreased packed cell volume and hemoglobin)		Weir and Fisher 1972	BX
Neurological									
23	Rat	(W)	3-14 wk		20.8			Settimi et al. 1982	BX
Developmental									
24	Rat	(F)	20 d			13.6[b] (reduced fetal weight)	28.4 (rib cage defects, increased resorptions)	Heindel et al. 1991	BA
25	Mouse	(F)	17 d		43.4	79 (reduced fetal body weight)	175.3 (skeletal effects, increased resorptions)	Heindel et al. 1991	BA
Reproductive									
26	Rat	(F)	30-60 d		50		100 (testicular atrophy, decreased enzymes)	Lee et al. 1978	BX
27	Rat	(W)	90 d		0.6			Dixon et al. 1976	BX
28	Rat	(F)	90 d			26 (partial testicular atrophy)	88 (complete atrophy of testes)	Weir and Fisher 1972	BA
29	Rat	(F)	60 d		25	50 (reduced testicular enzymes, reduced testicular and epididymal weight)		Dixon et al. 1979	BX

TABLE 2-2 (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Form
30	Rat	(F)	90 d			26 (partial testicular atrophy)	88 (complete atrophy of testes)	Weir and Fisher 1972	BX
31	Rat	(W)	70 d			44.7 (impaired spermatogenesis)		Seal and Weeth 1980	BX
32	Mouse	(F)	13 wk				288 (degeneration or atrophy of seminiferous tubules)	NTP 1987	BA
33	Mouse	(F)	27 wk		26.5	111 (impaired spermatogenesis, degeneration of seminiferous tubules)		NIEHS 1990	BA
34	Dog	(F)	38 wk			29 (testicular atrophy, spermatogenic arrest)		Weir and Fisher 1972	BX
35	Dog	(F)	90 d		4.4	44 (severe testicular atrophy)		Weir and Fisher 1972	BX
36	Dog	(F)	38 wk			29 (testicular atrophy, spermatogenic arrest)		Weir and Fisher 1972	BA
37	Dog	(F)	90 d		4.4	44 (severe testicular atrophy)		Weir and Fisher 1972	BA
CHRONIC EXPOSURE									
Death									
38	Mouse	(F)	103 wk				48 (40% mortality)	NTP 1987	BA
Reproductive									
39	Rat	(F)	2 yr		17.5		58.5 (atrophy of testes, decreased testes weight)	Weir and Fisher 1972	BX

TABLE 2-2 (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Form
40	Rat	(F)	3 gen		17.5		58.5 (atrophy of testes, decreased ovulation)	Weir and Fisher 1972	BA
41	Rat	(F)	3 gen		17.5		58.5 (atrophy of testes, decreased ovulation)	Weir and Fisher 1972	BX
42	Rat	(F)	2 yr		17.5		58.5 (atrophy of seminiferous tubule epithelium, decreased tubule size, decreased testicular weight)	Weir and Fisher 1972	BA
43	Mouse	(F)	103 wk		48		96 (testicular atrophy, interstitial hyperplasia)	NTP 1987	BA
44	Dog	(F)	2 yr		8.75			Weir and Fisher 1972	BX
45	Dog	(F)	2 yr		8.75			Weir and Fisher 1972	BA

[a]The number corresponds to entries in Figure 2-2.
[b]Used to derive an intermediate oral MRL of 0.01 mg/kg/day; dose divided by an uncertainty factor of 1000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

BA = boric acid; BX = borax; (C) = capsule; d = day(s); Derm/oc = dermal/ocular; (F) = feed; Gastro = gastrointestinal; gen = generation; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; Resp = respiratory; (W) = water; wk = week(s); yr = year(s)

FIGURE 2-2. Levels of Significant Exposure to Boron and Compounds – Oral

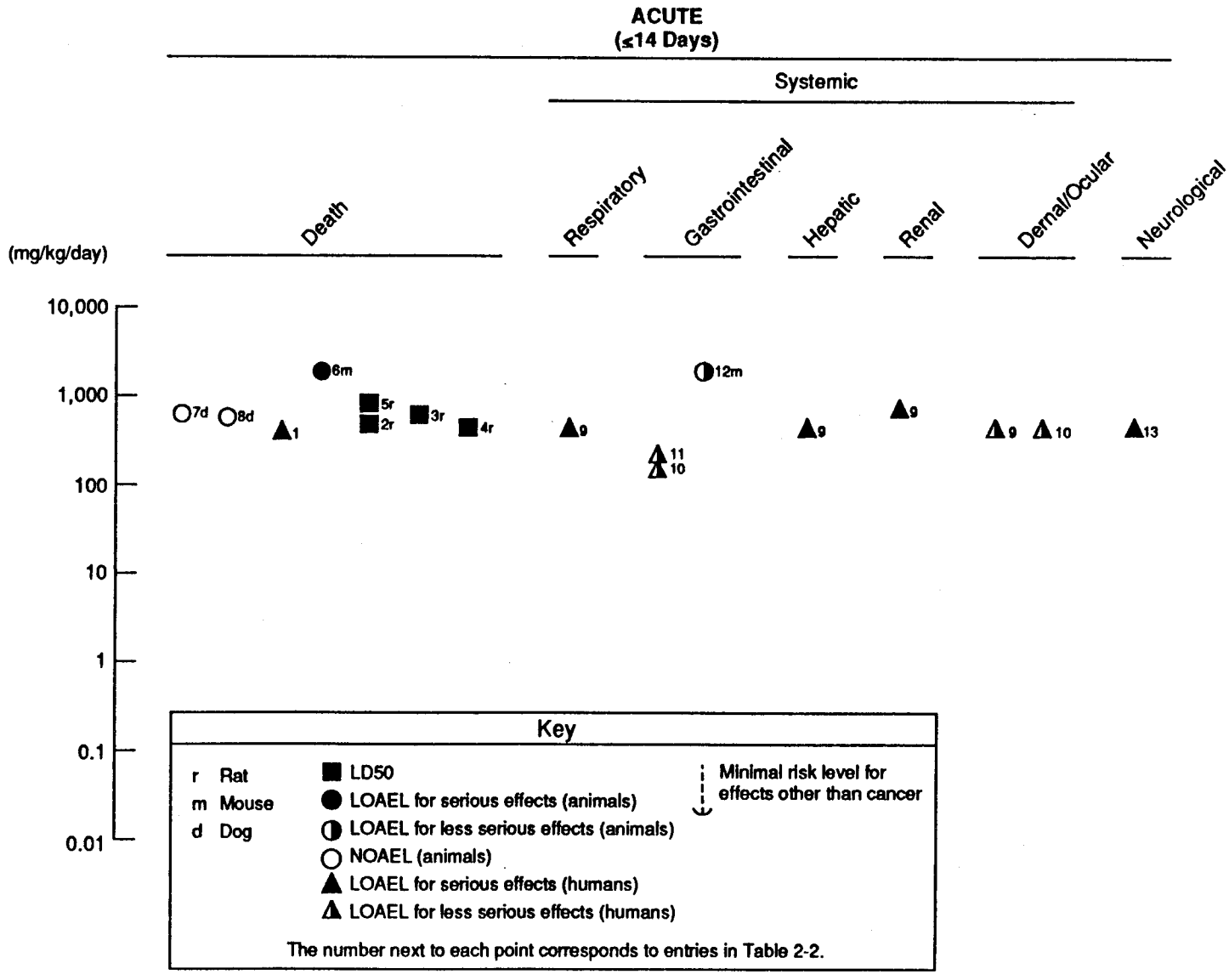


FIGURE 2-2 (Continued)

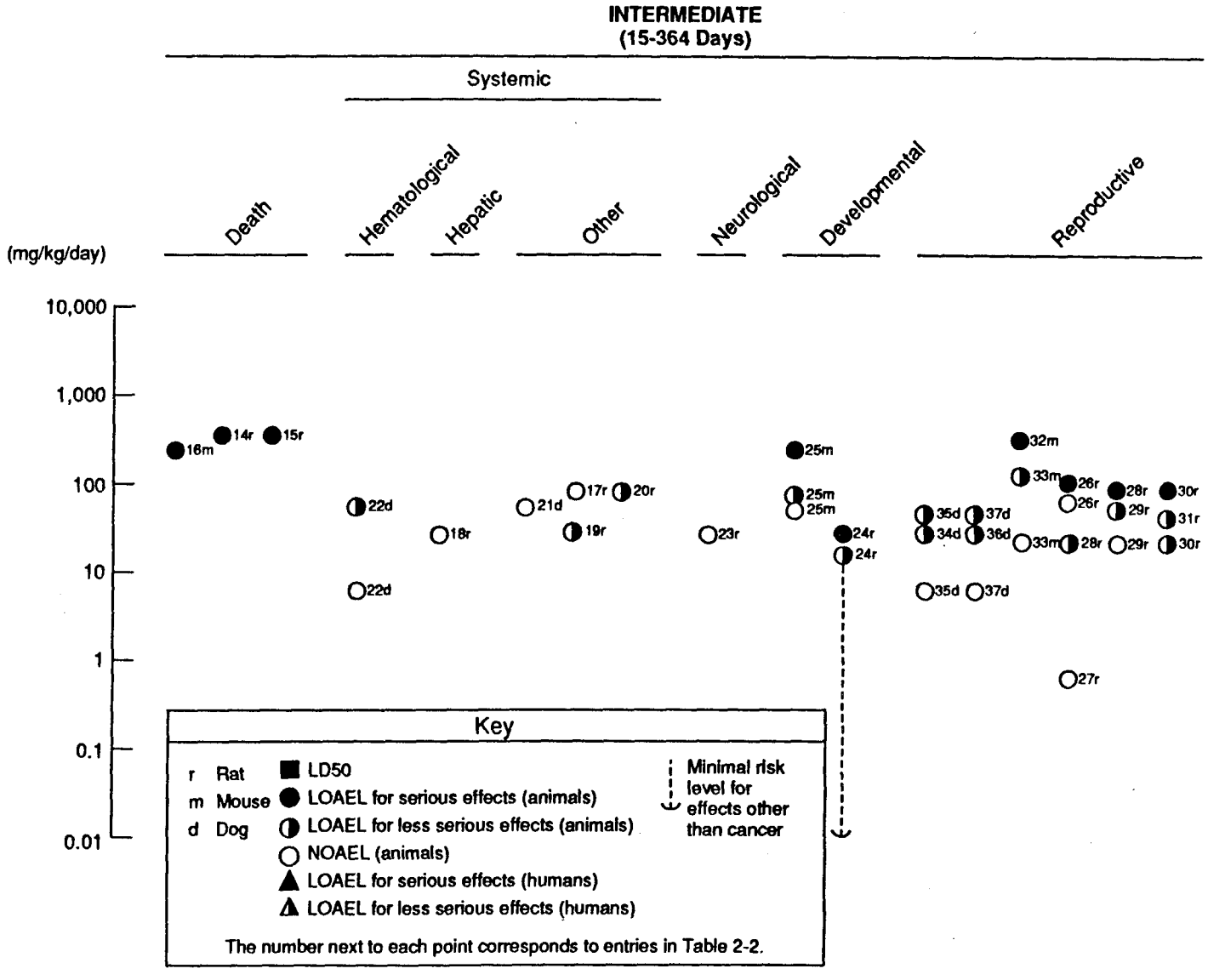
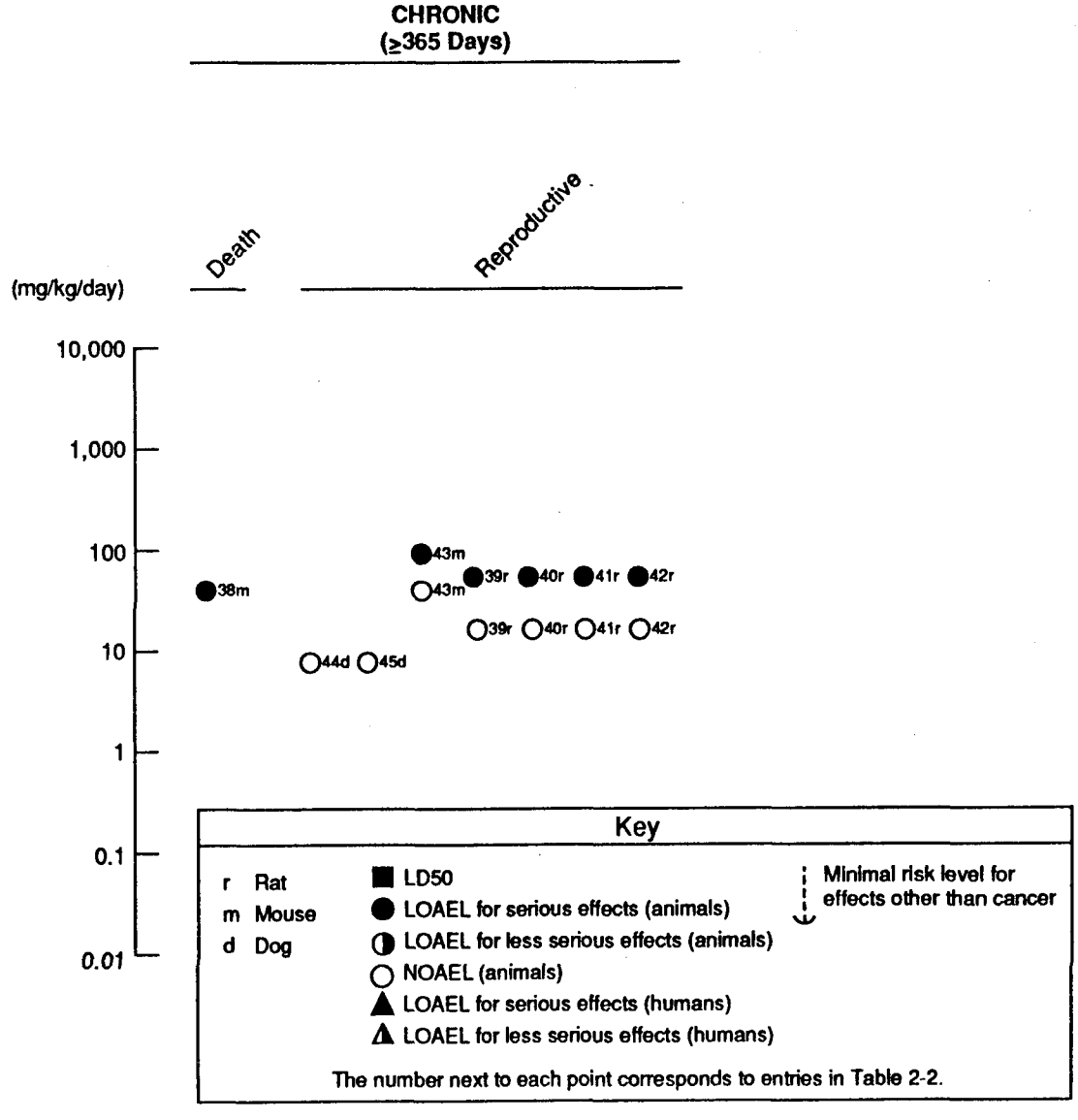


FIGURE 2-2 (Continued)



2. HEALTH EFFECTS

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 or greater (based on 1.9 kg body weight) as boric acid which was accidently incorporated in infant formula (Wong et al. 1964). Vomiting was the only sign-of boron toxicity in two adult females who had ingested 241 mg boron/kg/day as boric acid in a fungicide and 895 mg boron/kg of a boric acid-containing insecticide in a suicide attempt, The subjects were hospitalized for 24-96 hours and did not develop further symptoms following release (Linden et al. 1986).

Hematological Effects. Two male and three female dogs fed 44 mg boron/kg/day as borax had decreased packed cell volume and hemoglobin values. Erythrocyte count, total and differential leucocyte counts were comparable to control levels (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).

In rats given approximately 20.8 mg boron/kg/day as borax in drinking water, NADPH-cytochrome C reductase activity and cytochrome b, content decreased in the liver microsomal fraction after 10 and 14 weeks (Settimi et al. 1982). There was also a reduction in the cytochrome P-450 concentration detected at 14 weeks (Settimi et al. 1982).

Renal Effects. Human case reports involving high accidental ingestion levels show that boron can cause injury to the kidney. 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).

Dermal/Ocular 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 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, rats fed 88 and 263 mg boron/kg/day as borax or boric acid had inflamed eyes and skin desquamations on the paws and tails (Weir and Fisher 1972).

2.2.2.3 Immunological Effects

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

2.2.2.4 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 4-30 g borax for 4-10 weeks (O'Sullivan and Taylor 1983) and 9-125 g borax for 5-12 weeks (Gordon et al. 1973). Estimates of boron consumption could not be determined since the authors did not provide data on kilogram body weights. Blood boron levels in patients 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 borax for 3 months, the blood boron level was 1.64 mg/100 mL (Gordon et al. 1973).

In 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 RNA concentration and increased acid proteinase activity in brain occurred after 14 weeks (Settimi et al. 1982).

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

2.2.2.5 Developmental Effects

No studies were located regarding developmental effects in humans after oral exposure to boron.

In animals, fetotoxicity was observed in rats and mice The average fetal body weight per litter in rats was reduced in pups of dams administered 13.6 mg boron/kg/day or greater (78 mg/kg/day boric acid) on gestation days 0 to 20 (Heindel et al. 1991). Similarly, pups of mice administered 79 mg boron/kg/day (452 mg/kg/day boric acid) showed reduced body weight. Boron was also teratogenic in rats and mice. There was agenesis or shortening of rib XIII and the lateral ventricles of the brain were enlarged in rats at dose

levels of 28.4 mg boron/kg/day (163 mg/kg/day boric acid) or greater (Heindel et al. 1991). Skeletal effects were reported at the highest dose tested (175.3 mg boron/kg/day or 1,003 mg/kg/day boric acid) in mice. No effects were observed in the 43.4 mg boron/kg/day (248 mg/kg/day boric acid) dose group (Heindel et al. 1991). Based on a value of 13.6 mg boron/kg/day, an intermediate oral MRL of 0.01 mg/kg/day was calculated as described in the footnote on Table 2-2.

2.2.2.6 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to boron.

Animal studies demonstrated that boron can cause injury after intermediate and chronic exposure to the gonads in animals, especially the testes. Impaired spermatogenesis has been reported in rats administered 300 mg/boron/L as borax (44.7 mg boron/kg/day) in drinking water for 70 days (Seal and Weeth 1980), but no reproductive effects were evident in rats administered up to 6 mg boron/L of borax (0.6 mg boron/kg/day) in drinking water for 90 days (Dixon et al. 1976). While severe testicular atrophy was seen in dogs fed up to 44 mg boron/kg/day (1,750 ppm boron, as borax or boric acid) for 90 days (Weir and Fisher 1972), partial testicular atrophy in rats occurred at a dose of 26 mg boron/kg/day (525 ppm boron) (Weir and Fisher 1972). Degeneration or atrophy of the seminiferous tubules was demonstrated in mice fed 144 mg boron/kg/day as boric acid (5,000 ppm boric acid) (NTP 1987). In rats fed at least 50 mg boron/kg/day (as borax) up to 60 days, there were reduced testicular weight and germinal aplasia at 60 days (Dixon et al. 1979). In the same study, ≥50 mg boron/kg/day caused reduction in hyaluronidase, sorbitol dehydrogenase, and lactic acid dehydrogenase (isoenzyme-X) at 30 days and testicular and epididymal weights were reduced (Dixon et al. 1979).

In contrast, Lee et al. (1978) did not find significant adverse effects in male rats fed 50 mg boron/kg/day (as borax) for 30 and 60 days. Dogs were fed 29 mg boron/kg/day as borax and boric acid (1,170 ppm), respectively in the diet for 38 weeks (Weir and Fisher 1972). Testicular atrophy and spermatogenic arrest were reported. When dogs were administered 8.8 mg boron/kg/day (350 ppm borax or boric acid) for 2 years, no reproductive effects were observed (Weir and Fisher 1972). Reproductive effects were reported in rats following chronic exposure. In rats fed up to 58.5 mg boron/kg/day (as borax or boric acid) for several generations, there was a lack of viable sperm in atrophied testes and ovulation decreased in females (Weir and Fisher 1972). There were testicular atrophy and interstitial hyperplasia in mice that consumed lethal doses (48 and 96 mg boron/kg/day) over a period of 103 weeks. However, the authors did not specify cause of death (NTP 1987). In a 2-generation reproduction mouse study using continuous breeding protocol, there was degeneration of the seminiferous tubules and spermatogenesis was impaired at dose levels of 111 mg boron/kg/day (636 mg/kg/day boric acid) or greater. No effects were observed in the 27 mg boron/kg/day (152 mg/kg/day boric acid) dose group (NIEHS 1990).

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

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans and animals after oral exposure to boron. Genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

No studies were located regarding cancer in humans after oral exposure to boron.

In a life-time bioassay in which male and female $B6C3F_1$ mice consumed 48 mg boron/kg/day or 96 mg boron/kg/day as boric acid in the diet, there was no evidence of carcinogenicity (NTP 1987).

2.2.3 Dermal Exposure

2.2.3.1 Death

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

2.2.3.2 Systemic Effects

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

All reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 2-3.

Hematological Effects. Data are sparse in animals. It was reported in Draize and Kelley (1959) that 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/Ocular Effects. Animal studies show that boron oxide dust can affect the eye and skin. Instillation of boron oxide dust (50 mg) into the eyes of four rabbits produced conjunctivitis (Wilding et al. 1959). 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).

TABLE 2-3. Levels of Significant Exposure to Boron and Compounds - Dermal

Species	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Form
ACUTE EXPOSURE							
Systemic							
Rabbit	1 d	Derm/oc		13 (conjunctivitis)		Wilding et al. 1959	BO
		Derm/oc		1[a] (erythema)			

[a]Original unit provided by author was 1 g/cm^2.

BO = boron oxide; d = day; Derm/oc = dermal/ocular; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

2. HEALTH EFFECTS

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

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

Genotoxicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

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

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

No quantitative studies were located regarding absorption in humans or animals after inhalation exposure to boron. Reports of upper respiratory tract symptoms following exposure to boron oxide and boric acid dusts suggest boron can deposit in the upper airway (Garabrant et al. 1984, 1985).

2.3.1.2 Oral Exposure

No quantitative studies were located regarding absorption in humans or animals after oral exposure to boron and compounds. Gastrointestinal absorption was indicated in humans as evident by the urinary recovery of 93.9% of the ingested dose of boric acid when urine samples were calculated over a 96 hour period (Jansen et al. 1984a). Neurological, kidney, and liver damage following ingestion further suggest that boron can be absorbed (Wong et al. 1964).

2.3.1.3 Dermal Exposure

No quantitative studies were located regarding boron absorption in humans or animals after dermal exposure. Urinary excretion studies in humans (Section 2.3.4.3) suggest there is very little absorption of boron through intact skin. Excretion studies (Section 2.3.4.3) in rabbits suggest that boron is readily absorbed following contact with damaged skin (Draize and Kelley 1959).

2.3.2 Distribution

No quantitative studies were located regarding distribution in humans or animals after exposure to boron and compounds by the following routes:

2.3.2.1 Inhalation Exposure
2.3.2.2 Oral Exposure
2.3.2.3 Dermal Exposure

2.3.3 Metabolism

No studies were located regarding metabolism in humans or animals after exposure to boron or boron compounds by the following routes:

2.3.3.1 Inhalation Exposure
2.3.3.2 Oral Exposure
2.3.3.3 Dermal Exposure

2.3.4 Excretion

2.3.4.1 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).

2.3.4.2 Oral Exposure

Over 93% of the administered dose was excreted in the urine of six male human 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 (4-27.8). There was no correlation between half-life and calculated serum boric acid level at t, ($r=0.08$, $p=0.84$) (Litovitz et al. 1988). Boric acid was detected in urine of patients 23 days after a single ingestion (Wang et al. 1964).

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).

2.3.4.3 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 bw) 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).

2.3.4.4. Other 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/min 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).

2.4 RELEVANCE TO PUBLIC HEALTH

Estimates of levels of exposure to boron posing minimal risk to humans (MRLs) have been made. These are discussed in Section 2.2 and were based on data believed to be reliable for the most sensitive noncancer effect for each route and exposure duration. No data were located on effects of acuteduration inhalation exposure in humans or animals nor on intermediate-duration inhalation exposure to boron in humans. Available information on intermediate-duration inhalation exposure in animals and chronic-duration inhalation exposure in humans do not reliably identify the most sensitive target organ, No data on effects of acute-duration oral exposure to boron in humans or animals nor on intermediate exposure in humans were located. In animals, prenatal exposure of mice (79 mg boron/kg/day as boric acid) and rats (13.6 mg boron/kg/day as boric acid) during gestation days 0-17 and 0-20 caused developmental effects consisting of reduced fetal body weight or minor skeletal changes and possibly delay in maturation (Heindel et al. 1991). There was degeneration of the seminiferous tubules and impaired spermatogenesis in mice exposed to dose levels of 111 mg boron/kg/day as boric acid for 2 generations (NIEHS 1990). In other studies involving intermediate duration exposure, gonadal damage, primarily in the testes, was evident at dose levels from 26 to 288 mg/kg/day (NTP, 1987; Weir and Fisher 1972), but not at dose levels of 0.6 and 25 mg/kg/day (Dixon et al. 1976, 1979). Exposure of dogs to boron (as boric acid or borax) in the diet for 38 weeks caused testicular atrophy and spermatogenic arrest at dose levels of 29 mg boron/kg/day (Weir and Fisher 1972). Based on a LOAEL value of 13.6 mg boron/kg/day for developmental toxicity, an intermediate oral MRL of 0.01 mg boron/kg/day was derived using an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans and 10 for human variability). However, testicular effects were reversible within 25 days after compound treatment ceased. No effects were observed in rats fed diets containing doses up to 8.75 mg boron/kg/day) for 2 years (Weir and Fisher 1972). Because developmental toxicity occurred at dose levels less than those for reproductive toxicity, the intermediate MRL based on developmental toxicity'should be protective against reproductive toxicity following chronic

exposure. No data were located on effects of chronic-duration oral exposure in humans. A chronic MRL was not derived. Acute-duration, intermediateduration, and chronic-duration dermal MRLs were not derived for boron due to the lack of an appropriate methodology for the development of dermal MRLs.

No studies have been found regarding immunological effects of boron and compounds in humans or animals.

Death. Human studies have shown that boron can be lethal following short-term exposure. 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 (Locatelli et al. 1987; Wong et al. 1964). No data were found on the potential for boron to cause death in humans after intermediate and chronic inhalation and oral exposures. Liver, kidney, brain damage, and skin lesions have been found in lethal cases following ingestion of boron, but death has been attributable to respiratory failure. In other studies, chronic dermal exposure to boron in neonates was fatal (Litovitz et al. 1988). There appears to be a differential susceptibility with regard to death in adults. It has been postulated that increased competence of the adult kidney accounts for adult tolerance to boron. Based on these findings, lethality may be an area of concern following neonate exposure to boron.

Animal studies support human findings. Boron was lethal after ingestion for acute, intermediate, and chronic duration exposures (NTP 1987; Smyth et al. 1969; Weir and Fisher 1972).

Systemic Effects

Respiratory Effects. Symptoms of acute irritation of the upper airway were observed at borax and boric acid levels of 4 mg/m^3 or greater (Garabrant et al. 1984, 1985). No adverse respiratory effects were observed in humans following intermediate inhalation exposures. Chronic inhalation exposure caused irritation of the upper respiratory tract (Garabrant et al. 1984, 1985). There were no changes in the FEV_1 and FVC in borax workers (Wegman et al. 1991). Intermediate inhalation exposure in animals caused irritation of the nose (Wilding et al. 1959).

Gastrointestinal Effects. Boron or boron compounds can result in gastrointestinal disorders in humans following acute and intermediate oral exposures. Most of the studies focused on clinical symptoms including vomiting and diarrhea. No data were found on biochemical changes and limited data were provided on histopathological effects. Infants appear to be particularly susceptible to boron toxicity, possibly due to the fact that their detoxifying enzyme systems are immature and there is greater gastrointestinal absorption.

No studies were located in animals regarding gastrointestinal effects following boron exposure.

2. HEALTH EFFECTS

Hepatic Effects. No adverse hepatic effects have been reported in humans or animals following inhalation or dermal exposure to boron or boron compounds. Acute oral exposure in humans caused congestion, fatty changes, and parenchymatous degeneration (Wong et al. 1964). No data were available on biochemical changes. It is not clear how boron affects the liver; however, limited animal data suggest impaired electron transfer and macrometabolism. In studies with rats, boron interfered with flavin metabolism in flavoprotein dependent pathways (Settimi et al. 1982). It is not clear if similar effects will occur in humans.

Renal Effects. No adverse renal effects have been reported in humans or animals following inhalation of boron oxide, boric acid dust, or boron oxide aerosol. Similarly, dermal exposure to boric acid in humans or animals did not adversely affect the kidneys. Renal tubular damage has been observed, and there.was reduced urine output in infants who consumed 505 mg boron/kg in infant formula for 3-5 days (Wong et al. 1964). Since renal effects occurred in only a few cases and there is no confirming evidence in animals, the potential for boron to cause renal effects cannot be conclusively established.

Dermal/Ocular Effects. Human occupational exposure to boron oxide and boric acid dusts in workplace air irritated the eyes (Garabrant et al. 1984). Ingestion of large amounts of boron (505 mg boron/kg as boric acid) caused extensive exfoliative dermatitis in humans (Wong et al. 1964). The application of boric acid on the forearm of human subjects did not affect the skin (Draize and Kelley 1959). Rabbits developed erythema when boron oxide dust was applied to the skin and conjunctivitis was observed following contact with boron oxide dust (Wilding et al. 1959).

Immunological Effects. No studies were located regarding the effects of boron on the immune system in humans or animals after inhalation, oral, or dermal exposure. In the absence of effects on target organs and direct tests on immune function, the potential for boron to cause immunological effects in humans cannot be conclusively evaluated.

Neurological Effects. No adverse neurological effects have been observed in humans or animals following inhalation or dermal exposure. Acute and intermediate oral exposures to boron and boron compounds caused various neurological responses in humans. Degenerative changes in brain neurons which may have been an agonal effect were reported in one infant who consumed 505 mg boron/kg as boric acid for 3 days (Wong et al. 1964). At a higher dose (765 mg boron/kg), there was extensive vascular congestion, widespread perivascular hemorrhage, and intravascular thrombosis in another infant who ingested infant formula containing boric acid for 5 days (Wong et al. 1964). Biochemical changes have also been found. Cerebral succinate dehydrogenase activity was increased in rats that ingested borate in drinking water for lo-14 weeks, suggesting alteration in electron-transfer in the mitochondrial respiratory chain (Settimi et al. 1982). Increased RNA concentration and increased acid proteinase activity in the brain also occurred (Settimi et al. 1982). Altered metabolism and brain tissue redox state suggest changes in protein metabolism.

Based on these considerations, neurological damage is an area of concern following exposure to boron at toxic levels.

Developmental Effects. Developmental changes in rats and mice have been observed in offspring of dams exposed to 28.4 mg boron/kg/day and 175.3 mg boron/kg/day, respectively (Heindel et al. 1991). These effects have been observed at dose levels in the same range as those producing changes in spermatogenesis. No epidemiological studies were located regarding the effects of boron on the developing fetus. Although human data are lacking and there are no direct quantitative studies regarding placental transfer of boron, positive responses in two animal species suggest that developmental toxicity may be an area of concern in humans following exposure to boron. The LOAEL value of 13.6 mg boron/kg/day (Heindel et al. 1991) was used to calculate an intermediate oral MRL of 0.01 mg/kg/day as described in the footnote in Table 2-2.

Reproductive Effects. A study of 28 male workers exposed to borate aerosols during the production of boric acid revealed low sperm counts in six of these workers (Tarasenko et al. 1972). The authors reported exposure concentrations ranging from 22 to 80 mg/m^3. The overall reliability of these data is reduced due to the small study group, It should also be noted that low sperm count is a naturally occurring phenomenon. No studies were located regarding reproductive effects in humans after oral or dermal exposure.

In animals, boron affects gonads in dogs, rats, and mice. The testes are particularly susceptible after intermediate ingestion (44 and 29 mg boron/kg/day, respectively) (Seal and Weeth 1980; Weir and Fisher 1972). Following chronic oral exposure, no effects were observed at a dose of 8.75 mg boron/kg/day (Weir and Fisher 1972). In spite of the absence of reliable human data, limited evidence of reproductive effects in animals suggest that reproductive toxicity may be an area of concern following boron exposure in humans.

Genotoxic Effects. No studies were located regarding genotoxic effects of boron by inhalation, oral, or dermal exposure in humans and animals. Results were negative in bacterial assays and in the in vitro (Table 2-4) mammalian assays, including tests for chromosomal aberrations and gene mutation. Existing data suggest that genotoxicity is not an area of concern following exposure to boron in humans.

Cancer. No epidemiological studies were located associating cancer and boron exposure. In mice fed boron (as boric acid) for 103 weeks, the number of tumors observed did not differ significantly from untreated control levels (NTP 1987). In the absence of human data and studies from other animal species, and the lack of evidence of mutagenic activity, the carcinogenic potential of boron in humans cannot be determined conclusively.

TABLE 2-4. 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
S. typhimurium	Gene mutation	-	-	Benson et al. 1984
Escherichia coli	Gene mutation	-	-	Demerec et al. 1951
S. typhimurium	Gene mutation	-	-	NTP 1987
Mammalian cells:				
Mouse lymphoma	Gene mutation	-	-	NTP 1987
Chinese hamster ovary	Chromosomal aberration	-	-	NTP 1987

- = negative result

2. HEALTH EFFECTS

2.5 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). A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time biologic 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 and compounds are discussed in Section 2.5.1.

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 physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are often not 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 and compounds are discussed in Section 2.5.2.

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, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, "POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE."

2.5.1 Biomarkers Used to Identify and/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 pg/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 0.004 to 0.66 mg/100 mL (Imbus et al, 1963). In one infant, the urine contained 13.9 mg boron/L 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 human 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.

2.5.2 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.

2.6 INTERACTIONS WITH OTHER CHEMICALS

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

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

Neonatal children are unusually susceptible to boron exposure.

2.8 MITIGATION OF EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to boron. This section is intended to inform the public of existing clinical practice and the status of research concerning such methods. 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.

Human exposure to boron may occur by inhalation, ingestion, or dermal contact (see Chapter 5). 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 2.2). 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, they are flushed with water.

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, however, taken 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 request a control for convulsions.

Elemental boron is not metabolized (see Section 2.3). Studies in human 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 further 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; Stewart and McHugh 1990). Additional details regarding treatment of boron intoxication may be found in the cited references.

2.9 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 or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

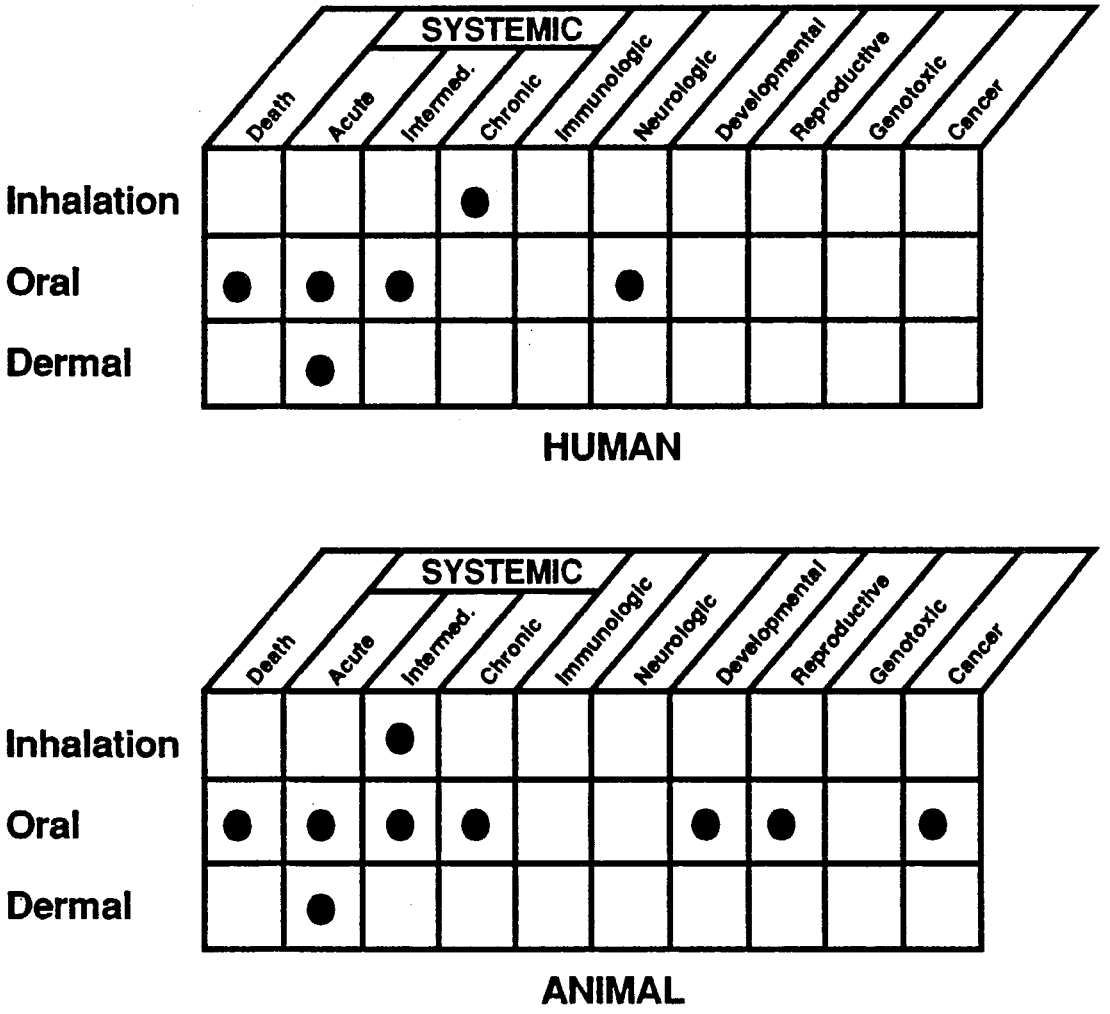
2.9.1 Existing Information on Health Effects of Boron

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to boron are summarized in Figure 2-3. 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 imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs" information.

Most of the information concerning health effects of boron in humans is found in case reports of accidental acute and intermediate ingestion of boron No information was found on effects after chronic ingestion. Those effects associated with inhalation occurred following chronic exposure in the workplace. No information was found on effects of boron after acute and intermediate inhalation exposures. Information on acute dermal exposure exist, but none was found on effects after intermediate and chronic exposures.

In animals, information exists on the acute, intermediate, and chronic ingestion of boron. Those effects associated with inhalation of boron occurred following intermediate exposures. No information was found on health effects of boron after acute and chronic inhalation exposures. Boron does cause health effects following acute dermal exposure. No information was found on health effects after intermediate and chronic dermal exposures.

FIGURE 2-3. Existing Information on Health Effects of Boron



● Existing Studies

2.9.2 Data Needs

Acute-Duration Exposure. There are data indicating mild upper respiratory irritation in humans from acute inhalation of borate dusts (Wegman et al. 1991). Information on the effects of a single oral exposure to boron compounds in humans and animals have provided data on lethal effects, while injury to the lungs, brain, kidneys, and liver have been reported in infants (NTP 1987; Smyth et al. 1969; Weir and Fisher 1972; Wong et al. 1964). Many of the human data are derived from case reports involving toxic effects in infants. No adverse health effects have been demonstrated in humans after dermal exposure. However, dermal/ocular effects have been associated with dermal exposure in animals (Wilding et al. 1959). The irritation effects observed were probably due to the exothermic rehydration reaction of the anhydride boron oxide. While existing data are sufficient to identify target organs, additional oral and dermal studies may clarify dose-response relationships in target tissues and identify a threshold for systemic effects due to a single-dose exposure. Human and animal data were not sufficient to derive acute oral and inhalation MRLs. Existing data provide qualitative evidence of toxic effects; however, data gaps exist relative to concentration and effects in the target tissues.

Intermediate-Duration Exposure. No studies were located in humans after intermediate exposure to boron compounds by any route of exposure. Borates are not absorbed through intact skin (Draize and Kelley 1959). No studies were available on dermal or inhalation exposure in animals; however, lethal effects and injury to the gonads, particularly the testes, have been demonstrated after oral exposure (Dixon et al. 1979; Lee et al. 1978; NIEHS 1990b; NTP 1987; Seal and Weeth 1980; Weir and Fisher 1972). Data suggest differences in sensitivity to boron compounds among animal species, with dogs more sensitive than rats or mice (Weir and Fisher 1972). Developmental effects were reported in mice and rats after oral exposure (Heindel et al. 1991). Data are sufficient to develop an intermediate oral MKL. The MRL was based on developmental toxicity in rats (Heindel et al. 1991). Although the MEL value is lower than the average daily intake of boron, it should be noted that recommended daily allowance levels have not been established for boron. Further studies by other routes of exposure would be useful in confirming target tissues (e.g., testes) and effects on the fetus identified by the primary exposure route. Also, these data may be used to further assess the level of confidence in current NOAEL and LOAEL values. Additional data may also provide some insight into the basis for differential susceptibility among species which may be useful in assessing potential human risk.

Chronic-Duration Exposure and Cancer. Limited epidemiologic studies conducted in humans demonstrated that borate dust can affect the upper respiratory tract and cause eye irritation following inhalation (Gabarant et al. 1984, 1985). Data were not sufficient to derive a chronic-duration MEL. No studies were found on oral and dermal exposures in humans. Oral studies in animals demonstrated injury to the gonads and to the developing fetus (NIEHS 1990a; NTP 1987; Weir and Fisher 1972). Existing oral studies are sufficient to rule out effects on other organ systems or tissues (NTP

1987; Weir and Fisher 1972). No studies were found on chronic dermal and inhalation data in animals. Additional studies are needed to identify critical effect levels. Although data are sufficient to develop a chronic oral MRL, a value was not derived. Because developmental toxicity occurred at dose levels less than those for reproductive effects, the intermediate MRL, which is based on developmental toxicity, should be protective against reproductive toxicity following chronic exposure. Additional studies would be useful in assessing the level of confidence in existing NOAEL and LOAEL values.

No epidemiologic studies have been conducted in humans regarding boron exposure and cancer. Well-designed and well-conducted case control or cohort studies would be useful in assessing risk to exposed humans. A long-term oral bioassay in mice was negative. No studies on chronic dermal or inhalation exposure evaluating carcinogenic potential in animals are available. The absence of effects in one species is not sufficient to rule out the potential to cause cancer. Additional chronic studies of other species and various doses would increase the level of confidence in results reported in existing studies.

Genotoxicity. No in vivo human data were located. Bacterial and limited mammalian assays were negative (Benson et al. 1984; Demerec et al. 1951; Haworth et al. 1983; NTP 1987). Considering the absence of mutagenic effects in bacterial and mammalian tests evaluating gene mutation and chromosomal aberrations, genotoxicity may not be an area of concern in humans. Based on existing data, additional studies are not needed at this time.

Reproductive Toxicity. No studies were found on the effects of boron compounds on the reproductive system in humans by any route of exposure. Oral studies in animals demonstrated injury to gonads, particularly the testes (Dixon et al. 1979; Lee et al. 1978; NIEHS 1990; Seal and Weeth 1980; Weir and Fisher 1972). No studies were found on chronic dermal and inhalation studies in animals. Sufficient data exist on the potential for boron compounds to affect male reproductive organs in animals (NIEHS 1990; NTP 1987; Weir and Fisher 1972). Data suggest that the severity of effects are species specific (Weir and Fisher 1972). Additional studies would be useful to clarify dose response relationships. Data suggest the female reproductive system is less susceptible and is affected only at very high dose levels (NIEHS 1990; NTP 1987; Weir and Fisher 1972). Additional studies evaluating reproductive effects in females may not be needed at this time.

Developmental Toxicity. No studies were found on the developmental effects of boron and compounds in humans following inhalation, oral, or dermal exposure. No data are available on the ability of boron to cross the placenta or accumulate in fetal tissue. Studies in rats and mice indicate delayed development and structural defects, primarily in the rib cage, following continuous oral exposure in the diet during pregnancy (Heindel et al. 1991). Existing animal data suggest additional testing would be useful in assessing potential risk to humans.

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 durations would 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. Studies of workers exposed to boron compounds demonstrated that boron can cause mild irritation of the eyes and respiratory tract (Garabrant et al. 1984, 1985). Other human studies involve case reports of accidental or intentional ingestion of large quantities of boron compounds (Litovitz et al. 1988; Locatelli et al. 1987). The studies identified key health effects (lung, kidney, brain, and liver) associated with boron exposure (Wong et al. 1984). Animal studies indicated the testes as a target tissue, Epidemiological studies of the birth rate of occupationally-exposed workers is currently underway at a major U.S. borate production facility (U.S. Borax and Chemical Corporation 1991).

Biomarkers of Exposure and Effect. Blood and urine borate concentrations are useful biomarkers of exposure (Jansen et al. 1984a; Litovitz et al. 1988). The gastrointestinal tract, skin, and brain are principal target organs following boron exposure in humans. Studies in animals demonstrate that boron compounds can also cause gonadal injury, particularly to the testes (Weir and Fisher 1972). Existing animal studies have established this effect as the most sensitive endpoint following oral exposure. Studies to determine other biomarkers would be useful in assessing the potential human health risk.

Absorption, Distribution, Metabolism, and Excretion. No quantitative information is available on the absorption, distribution, and metabolism of boron compounds; however, there are studies on the excretion of boron following oral (Jansen et al. 1984a; Litovitz et al. 1988) and inhalation (Wilding et al. 1959) exposures and after dermal exposure (Draize and Kelley 1959). Since data on toxicokinetics of boron are limited, additional studies are needed by all routes of exposure that will provide data on absorption rates, extent of conversion in the body and amount and rate of accumulation in various tissues. 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 (Dixon et al. 1979; Lee et al. 1978; NIEHS 1990; Seal and Weeth 1980; Weir and Fisher 1972). Data suggest differences in species sensitivity, with dogs more sensitive than rats and mice (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 would be useful in assessing differences in species sensitivity, and provide a better basis for extrapolation of animal data to human exposure risk.

Mitigation of 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 would be useful in determining the safety and effectiveness of possible methods for treating boron-exposed populations in the vicinity of hazardous waste sites.

2.9.3 On-going Studies

The National Institute of Environmental Health Sciences (J. Williams, investigator) is conducting a study on the disposition of boric acid in selected target and nontarget tissues. The potential of boric acid to cause in vivo riboflavin deficiency as a mechanism of the testicular toxicity is being investigated, as are the direct effects of boric acid applied to sertoli or leydig cells in primary culture from naive rats (CRISP 1990).

3. CHEMICAL AND PHYSICAL INFORNATION

3.1 CHEMICAL IDENTITY

Table 3-1 lists common synonyms, trade names, and other pertinent information to identify boron and selected compounds.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Table 3-2 lists important physical and chemical properties of boron and selected compounds.

TABLE 3-1. Chemical Identity of Boron and Compounds[a]

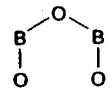
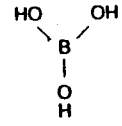
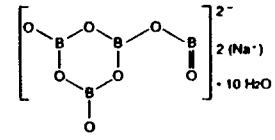
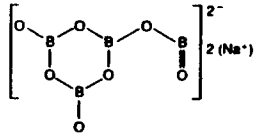
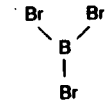
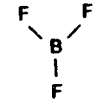
Characteristic	Boron	Boron oxide	Boric acid	Borax
Synonyms	No data	Boric anhydride; diborontrioxide	Boracic acid; orthoboric acid	Borax decahydrate; tincal; polybor
Trade name	No data	No data	No data	No data
Chemical formula	B	B_2O_3	H_3BO_3	$Na_2B_4O_7 \cdot 10H_2O$
Chemical structure[b]	Not applicable			
Identification numbers:				
CAS Registry	7440-42-8[d]	1303-86-2	10043-35-3	1303-96-4[d]
NIOSH RTECS	ED7350000[e]	ED7900000[e]	ED4550000[e]	VZ2275000[e]
EPA Hazardous Waste	No data	No data	No data	No data
OHM/TADS	7216607[f]	No data	7216606[f]	No data
DOT/UN/NA/ IMCO Shipping	No data No data	No data No data	No data No data	No data No data
HSDB	4482[f]	1609[f]	1432[f]	0328[f]
NCI	No data	No data	No data	No data

TABLE 3-1 (Continued)

Characteristic	Borax, anhydrous	Boron tribromide	Boron trifluoride
Synonyms	Borax, dehydrated; sodium tetraborate, anhydrous	Boron bromide	Boron fluoride
Trade name	No data	No data	No data
Chemical formula	$Na_2B_4O_7$	BBr_3	BF_3
Chemical structure[b,c]			
Identification numbers:			
CAS Registry	1303-96-4	10294-33-4	7637-07-2
NIOSH RTECS	VZ2275000[e]	ED7400000[e]	ED2275000[e]
EPA Hazardous Waste	No data	No data	No data
OHM/TADS	No data	No data	No data
DOT/UN/NA/ IMCO Shipping	No data No data	UN2692[f] No data	UN1008[f] IMCO 2.3
HSDB	0328[f]	0327[f]	0325[f]
NCI	No data	No data	No data

[a]All information obtained from Sax and Lewis 1987, except where noted.
[b]Grayson 1985
[c]Morrison and Boyd 1983
[d]EPA 1987b
[e]Sittig 1985
[f]HSDB 1989

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

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

Property	Boron	Boron oxide	Boric acid	Borax
Molecular weight	10.81	69.62	61.83	381.37
Color	Black or brown	Colorless	Colorless	Colorless
Physical state	Solid	Solid	Solid	Solid
Melting point	2300°C	450±2°C	169°C±1 tr to HBO_2	75°C, $-8H_2O$, 60°C
Boiling point	2550°C	1500°C[b]	$-1½H_2O$, 300°C	$-10H_2O$, 320°C
Density at 20°C	2.34	2.46	1.435 at 15°C	1.73
Odor	No data	No data	Odorless[b]	Odorless[c]
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water	Insoluble	Soluble in hot water; slightly soluble in cold water	63.5 g/L at 30°	20.1 g/L at 0°C
Organic solvents	Soluble in nitric and sulfuric acid[b]	Soluble in alcohol[b]	Soluble in alcohol, glycerol	Slightly soluble in alcohol, glycerol
Partition coefficients:				
Log octanol/water	No data	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data
Vapor Pressure	1.56×10^{-5} atm at 2140°C[e]	No data	No data	No data
Henry's law constant	No data	No data	No data	No data
Autoignition temperature	No data	Noncombustible[b]	Noncombustible[b]	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors	No data	No data	No data	No data

TABLE 3-2 (Continued)

Property	Borax, anhydrous	Boron tribromide	Boron trifluoride
Molecular weight	201.22	250.52	67.81
Color	Colorless	Colorless	Colorless
Physical state	Solid	Liquid	Gas
Melting point	741°C	-46°C	-126.7°C
Boiling point	Decomposes at 1575°C	91.3±0.25°C	-99.9°C
Density at 20°C	2.37	1.69 at 15°C[b]	2.99 g/L
Odor	Odorless[c]	No data	Pungent[c]
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	4.5 mg/m^3[d]
Solubility:			
Water	10.6 g/L at 0°C; 87.9 g/L at 40°C	Decomposes	1060 g/L at 20°C
Organic solvents	Insoluble in alcohol	Soluble in alcohol, CCl_4	Soluble in sulfuric acid
Partition coefficients:			
Log octanol/water	No data	No data	No data
Log K_{oc}	No data	No data	No data
Vapor Pressure	No data	100 mmHg at 33.5°C[f]	40 mmHg at -131.0° (solid) 760 mmHg at -110.7°C (liquid)[f]
Henry's law constant	No data	No data	No data
Autoignition temperature	Noncombustible[b]	No data	Noncombustible[b]
Flashpoint	No data	No data	No data
Flammability limits	No data	No data	No data
Conversion factors	No data	No data	No data

[a]All information obtained from Weast 1985, except where noted.
[b]Sax and Lewis 1987
[c]ACGIH 1986
[d]Ruth 1986
[e]Windholz 1983
[f]HSDB 1989

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

Boron is produced by the chemical reduction of boron compounds with reactive metals, either by nonaqueous electrolytic reduction or through thermal decomposition. Highly purified boron is produced by zone-refining or other thermal techniques (HSDB 1989; Stokinger 1981; U.S. Bureau of Mines 1989).

The United States produces most of the world's borates. Production figures for 1988 report 566,093 metric tons of boric oxide equivalent was produced from the mining of boron-containing minerals. Domestic production has remained relatively constant over the last 5 years ranging from a low of 570,629 metric tons in 1986 to a high of 625,061 metric tons in 1987 (Ferguson et al. 1982; U.S. Bureau of Mines 1989).

United States Borax 6 Chemical Corporation continues to be the primary world supplier of sodium borates. U.S Borax mines and processes crude and refined sodium borates, their anhydrous derivatives, and anhydrous boric acid at its plant, in Kern County, Boron, California. A second plant at Boron, California uses a proprietary process to produce technical-grade boric acid.

Kerr-McGee Chemical Corporation operates the Trona and Westend plants at Searles Lake, in San Bernardino County, to produce refined sodium borate compounds and boric acid from the mineral-rich lake brines.

4.2 IMPORT/EXPORT

The United States imported 59,875 metric tons of borax, boric acid, and the boron-containing minerals colemanite and ulexite in 1988 (U.S. Bureau of Mines 1988). As the world's largest producer of boron compounds, the United States exported 589,680 metric tons of boric acid and borates in 1988.

4.3 USE

Borates have diverse uses. Their principal uses (56%) are in the production of glass and glass products such as textiles.and insulating fiberglass. It is also used to make the enamels and glazes used as coatings on household and industrial products. Borates are used in herbicides, insecticides, soaps and cleansers, cosmetics, antifreeze, and leather tanning. Borax and boric acid are used in atomic reactors as a neutron absorber (EPA 1986b; HSDB 1989; Stokinger 1981: U.S. Bureau of Mines 1989).

4.4 DISPOSAL

No federal regulations were located which control the disposal of borates including sodium borates and boric acid. No quantitative disposal data *were* located.

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Boron is a naturally-occurring element found combined with other elements throughout the environment. Boron is neither transformed nor degraded in the environment, although changes in the specific form of boron and its transport may occur, depending on environmental conditions. It is estimated that natural weathering is a significant source of environmental boron.

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.

The EPA has identified 1,177 NPL sites. Boron, borate, and borax have been found at 21, 1, and 1, respectively, of the sites evaluated for these chemicals. However, we do not know how many of the 1,177 NPL sites have been evaluated for the presence of these chemicals. As more sites are evaluated by the EPA, these numbers may change (View 1989). The frequency of these sites within the United States can be seen in Figure 5-1.

5.2 RELEASES TO THE ENVIRONMENT

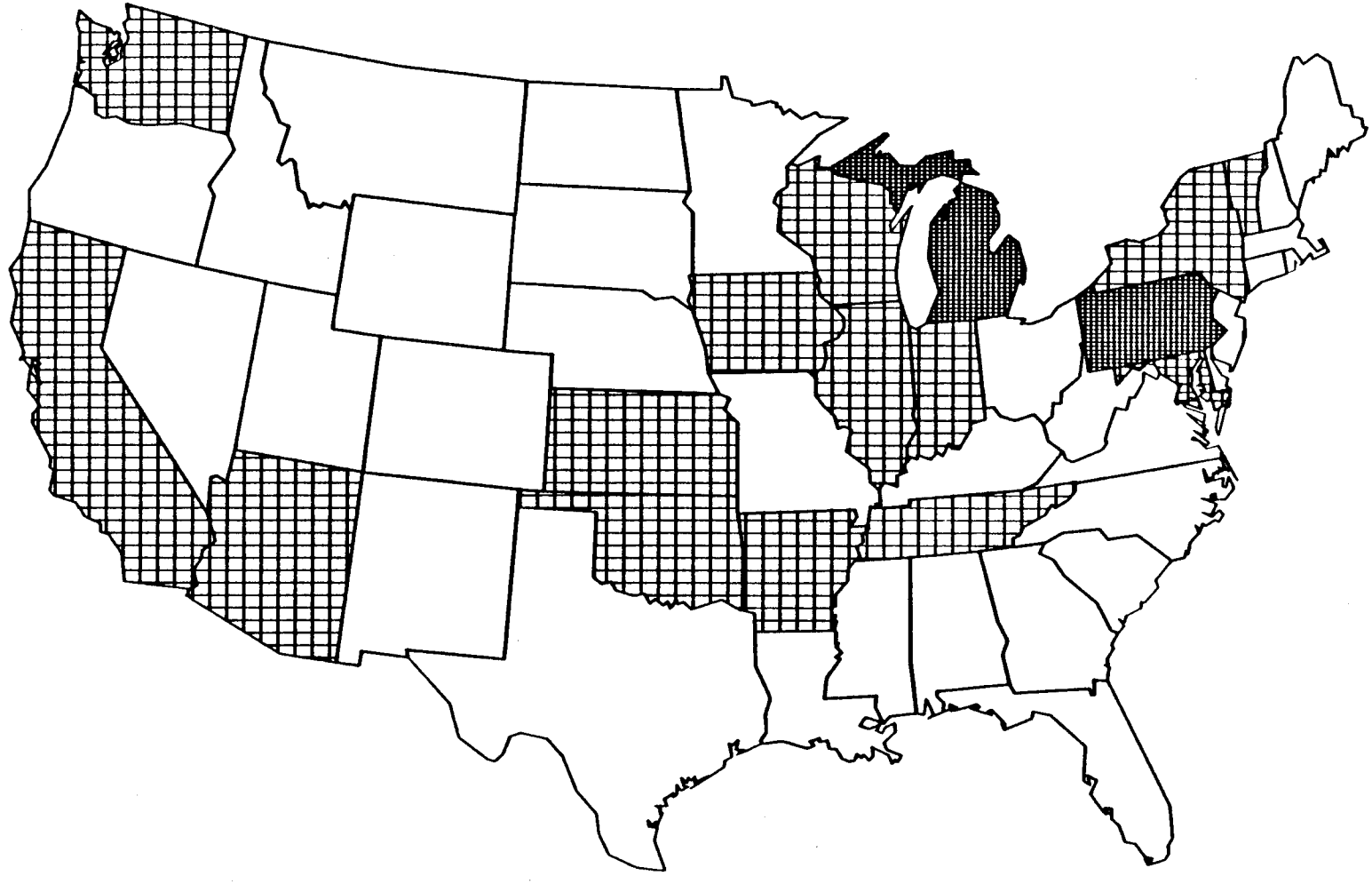
Borates are widespread, naturally-occurring substance found mainly as an inorganic compound in sediments and sedimentary rock. It is released to the environment slowly in low concentrations by weathering processes. Although few data are available quantifying boron releases from industrial sources, it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

Releases of boron to the environment occur from the production and use of boron and boron-related compounds. However, neither boron nor boronrelated compounds are listed on the Section 313 toxic chemical list and, therefore, are not included in the Toxics Release Inventory (TRI).

5.2.1 Air

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 coalfired 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). No quantitative data regarding boron releases to air were located.

FIGURE 5-1. FREQUENCY OF NPL SITES WITH BORON CONTAMINATION *



* Derived from View 1989

5.2.2 Water

Natural weathering of boron-containing rocks is a major source of boron compounds in water (Butterwick et al. 1989). The quantity of boron released varies widely with the geographic variations in boron-rich deposits. In the United States, the area richest in natural boron deposits is the Mojave Desert in California (Butterwick et al. 1989; Stokinger 1981).

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 concentration of 1 mg boron/L was reported in sewage effluents in California (Butterwick et al. 1989). No other quantitative data regarding boron releases to water in the United States were located. However, 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.

Boron has been detected in surface water and groundwater at hazardous waste sites. Data from the Contract Laboratory Program (CLP) Statistical Database indicate that boron occurred at about 20% of the sites at a geometric mean concentration of 156 ppb (0.156 mg boron/L) in positive samples of groundwater and at about 5% of the sites at a geometric mean of 1,177 ppb (1.177 mg boron/L) in surface water (CLPSD 1989).

5.2.3 Soil

Boron is naturally released to soil and water by rainfall, weathering of boron-containing minerals, desorption from clays and by decomposition of boron-containing organic matter. Man-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).

No quantitative data were located regarding man-made releases of boron compounds to soil. However, 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.

Data from the CLP Statistical Database indicate boron was detected in soil at about 5% of hazardous waste sites at a geometric mean concentration of 8,055 ppm in positive samples (CLPSD 1989). However, earlier data from the CLPSD (1980-1983) indicate a geometric mean concentration of boron of 21 mg/kg and a maximum concentration of 320 mg/kg (Eckel and Langley 1988), essentially equivalent to reported background levels of boron in soil. Clarification of

the discrepancy in the data is necessary in order to compare boron levels at hazardous waste sites to background levels.

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

Boron is a nonvolatile metalloid that occurs in combination with most of the other elements known (Cotton and Wilkinson 1980). 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 H_3BO_3 and the monovalent ion B(OH),. 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. Waggott (1969), for example, noted that boron is not significantly removed during the conventional treatment of waste water. Boron may, however, be co-precipitated with aluminum, silicon, or iron to form hydroxyborate compounds on the surfaces of minerals (Biggar and Fireman 1960).

Water borne boron may be adsorbed by soils and sediments. Adsorptiondesorption 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 et al. 1981; Keren and Mezuman 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 a 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 less than 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. Boron in water is completely absorbed by the human system, but it does not accumulate in body tissues (Waggott 1969). No other experimentally measured BCFs were located. LD

5.3.2 Transformation and Degradation

5.3.2.1 Air

There is no information available that suggests that particulate boron compounds are transformed or degraded in the atmosphere.

5.3.2.2 Water

Elemental boron is inert in the presence of water. Boron compounds rapidly transform to borates, the naturally occurring form of boron, in the presence of water. No further degradation is possible. Borate and boric acid are in equilibrium depending only on the pH of the water. If dissolved in atmospheric water, the standard borate-boric acid equilibria are established.

5.3.2.3 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 5.2.3). Borates are removed from soils by water leaching and by assimilation by plants.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

There are few studies made to estimate the concentration of boroncontaining compounds in ambient air. This is partly due to difficulties of analysis at the low levels involved. 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 of about 75 mg/kg boron.

5.4.2 Water

Boron is widely distributed in surface water and groundwater. Average surface water concentration in the United States is about 0.1 mg boron/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 boron/L. Mean concentrations calculated for the 15 drainage basins in the continental United States ranged from 0.019 mg boron/L in the Western Great Lakes Basin to 0.289 mg boron/L in the Western Gulf Basin (Butter-wick et al. 1989). 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 boron/L in coastal drainage waters to 360 mg boron/L in a boron-rich lake (Butter-wick et al. 1989; Deverel and Millard 1988). Mean boron concentration in a California river ranged from 0.30 to 0.50 mg boron/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 boron/L with a median concentration of about 4 mg boron/L (Butterwick et al. 1989; Deverel and Millard 1988). Waggott (1969) reports that groundwater boron concentrations greater than 100 mg/L are common in California.

Drinking water surveys generally do not report boron concentration. However, 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 less than 0.005 to greater than 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 less than 1 mg/L. The maximum level measured was 3.28 mg/L (McCabe et al. 1970).

5.4.3 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). Boron was detected in soils in Idaho at geometric mean concentrations of 4.6-9.8 mg/kg (Rope et al. 1988) and in sediments of Puget Sound (Malins et al. 1984).

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 (Butter-wick et al. 1989).

5.4.4 Other Environmental Media

Boron is assimilated by plants from soil and is therefore a natural constituent of many foods, mainly fruits and vegetables. The amount of boron absorbed varies considerably among different plant species (Butterwick et al. 1989). The Food and Drug Administration (FDA) has set a tolerance limit of 8 ppm boron for citrus fruit (21 CFR 180.271).

Boron compounds are present in several consumer products. Sodium borate and boric acid are widely used in cosmetics. Over 600 cosmetic products,including makeup, skin and hair care preparations, and shaving creams, contain these compounds at concentrations of up to 5% (Beyer et al. 1983). These compounds have also been used in insecticide powders for roach control, in medicines applied to the skin at concentrations up to 5% (Beyer et al. 1983) and in some laundry products (Butterwick et al. 1989; Stokinger 1981; Waggott 1969).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Human exposure to borates may occur through ingestion of food and water or insecticides used to control cockroaches, powders or dusts,inhalation of boron-containing or absorption of boron from cosmetics or medical preparations through mucous membranes or damaged skin. The most appreciable boron exposure to the general population is likely to be ingestion of food and to a lesser extent in water. Estimates of average daily boron ingestion by humans range from 10 to 25 mg (Beyer et al. 1983; Waggott 1969).

Occupational exposure to boron compounds may be higher. Workers in industries producing or using boron or boron compounds may be exposed by inhalation to boron-containing dusts or gaseous boron compounds due to process upsets or faulty equipment. Dermal absorption of boron may also occur if damaged skin is in contact with these materials, but this is considered a minor pathway (Stokinger 1981).

Borate dusts have been monitored in workplace air. 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 (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 (Garabrant et al. 1984). These values indicate that permissible exposure limits (PELs) set by OSHA, or threshold limit values (TLVs) recommended by the ACGIH, for boron-containing dusts in workplace air (Table 7-l) may, at times, be exceeded. Other industries include manufacture of fiberglass and other glass products, cleaning and laundry products, fertilizers, pesticides, and cosmetics (U.S. Borax and Chemical Corporation 1991; Stokinger 1981).Median normal values of boron in human blood (9.76 μg/100 g) and urine samples from these workers (720 μg boron/L) were reported (Stokinger 1981). Boron was not detected in a national survey of human adipose tissue (Stanley 1986). The National Institute for Occupational Safety and Health (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 NOHS nor the 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 the number of workers potentially exposed to borax at 2,490,000, to boron oxide at 21,000, and to boron trifluoride at 50,000.

5.6 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). Infants may be at risk in homes where boric acid containing roach powder on floor parameters is used to control cockroaches.

Workers in industries producing or using boron-containing materials also have potentially high exposure as noted above (Section 5.5). People living in the vicinity of waste sites are also at risk of higher-than-normal exposure levels.

5.7 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCIA, 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 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 or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

5.7.1 Data Needs

Physical and Chemical Properties. The solubilities of many boron minerals are not known precisely, but this lack of detailed information may not be a major limitation, since it appears unlikely that mineral equilibria significantly influence the fate of boron in the environment.

5. POTENTIAL FOR HUMAN EXPOSURE

Production, Import/Export, Use, and Disposal. The production volume and uses of boron and boron compounds are well documented (Ferguson et al. 1982; HSDB 1989; U.S Bureau of Mines 1989). However, data on disposal methods and volume would allow better estimation of human exposure to boron from this source.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1987, became available in May of 1989. However, neither boron nor boron-related compounds are currently listed in the database. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate. The only quantifiable mechanism that influences the fate of boron is soil adsorption (Rai et al. 1986). Additional research with soils that do not have significant quantities of aluminum and iron oxide may provide a more comprehensive view of the mobility of boron in the environment.

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; CLPSD 1989). While exposure can occur by these routes, quantitative data on amounts absorbed or are bioavailable would be useful in clarifying the toxic potential of boron in humans.

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.

Exposure Levels in Environmental Media. Data on boron levels in surface water and soil are extensive (Butterwick et al. 1989; Eckel and Langley 1988; EPA 1986b), but additional data on air, food, and drinking water concentrations of boron would be useful in increasing the accuracy of human exposure estimates.

Exposure Levels in Humans. Normal levels of boron in human blood and urine have been reported (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.

Exposure Registries. No exposure registries for boron were located. This compound is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The compound will be

considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to the exposure to this compound.

5.7.2 On-going Studies

No information was located on any on-going studies on the fate, transport, or potential for human exposure for boron.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting and/or measuring and monitoring boron in environmental media and in biological samples. The intent is not to provide an exhaustive list of analytical methods that could be used to detect and quantify boron. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used to detect boron in environmental samples are the methods approved by federal agencies 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 refine previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

6.1 BIOLOGICAL MATERIALS

Methods for the determination of boron in samples of toxicological interest have been summarized (Stokinger 1981; Van Ormer 1975). Usually total boron is determined, although in limited cases specific boron species can be determined as well. Boron is very poorly measured by atomic absorption analysis. High-temperature atomic spectrometric methods, especially inductively coupled plasma atomic emission spectrometry, including atomic emission spectrography, work well for boron. Colorimetry and prompt neutron activation analysis can also be used.

Methods for the determination of boron in biological materials are summarized in Table 6-l.

Normally, for determination in biological samples, the sample is digested or ashed, and the boron is measured by atomic spectrometric determination.

6.2 ENVIRONMENTAL SAMPLES

Methods for the determination of boron in environmental samples are summarized in Table 6-2.

Boron is readily measured in multielement analyses of air, water, and solid waste samples by inductively coupled plasma (ICP) atomic emission spectroscopy, the method of choice for the determination of boron in modern practice. Although not multielement procedures, calorimetric cucumin and calorimetric carmine methods are still reliable methods for the determination of boron in water, air and solid waste samples. These calorimetric procedures provide adequate methods when ICP instrumentation is not available.

TABLE 6-1. Analytical Methods for Determining Boron in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood and urine	Ashed, dissolved in HCl	SA	5 µg/100g blood 40 µg/L urine	No data	Imbus et al. 1963
Blood	Ashed by oxygen in a Parr bomb, dissolved	Colorimetric carmine method	<0.1 µg/mL	84% at 5 µg/mL	Hill and Smith 1959
Serum (borate)	Deproteinized, allowed to react with reagent	Colorimetric carmine method	>endogenous levels which are <20 mg/L	92%-104%	Baselt 1988
Blood	Ashed, dissolved	Electrophoresis	No data	No data	Hill et al. 1957
Biological material[a]	Acid digestion	ICP/AES	5 µg/L[b]	No data	EPA 1986a

[a]This method is for water, sediments, and wastes.
[b]Method detection limit. Actual detection limits for boron in waste samples may be considerably higher.

ICP/AES = inductively coupled plasma atomic emission spectroscopy; HCl = hydrochloric acid; SA = atomic spectrographic analysis

TABLE 6-2. Analytical Methods for Determining Boron in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Collection on filter, workup in acid	ICP/AES	1 µg per sample	103% recovery	NIOSH 1984
Air for boron carbide	Collection on filter, ashed, suspended in 2-propanol, redeposited on silver membrane filter	x-ray powder diffraction	0.05 mg	No data	NIOSH 1985a
Water	Direct analysis	Colorimetric curcumin	0.2 µg	23% RSD	APHA 1985a
Water	Ash, dissolve in acid	Colorimetric carmine	2 µg	36% RSD	APHA 1985b
Water	Acidify, inject	ICP/AES	0.3 µg/L	No data	APHA 1985c
Water	Direct analysis	Colorimetric curcumin	0.2 µg	23% RSD	EPA 1983
Water	Filter, acidify	ICP/AES aspiration	5 µg/L	No data	EPA 1982
Sediments, solid wastes, sludges	Acid digestion	ICP/AES	5 µg/L[a]	No data	EPA 1986a

[a]Method detection limit. Actual detection limits for boron in waste samples may be 1-3 orders of magnitude higher.

ICP/AES = inductively coupled plasma atomic emission spectroscopy; RSD = relative standard deviation

6. ANALYTICAL METHODS

6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of boron is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 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 or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.3.1 Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Boron can be determined sensitively and selectively by inductively coupled plasma atomic emission analysis (EPA 1986a; Imbus et al. 1963). This method of analysis requires that the analyte be placed in solution, which canbe a problem with some of the more refractory boron species. With the exception of boron carbide (NIOSH 1985a), methods are lacking for the determination of specific boron compounds.

Methods for the determination of metabolites of boron in biological materials would be useful in studying the toxicity and metabolism of this element.

More specific methods for biomarkers of exposure would be helpful in toxicological studies of boron.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Inductively coupled plasma atomic emission spectrometry is the only satisfactory multielement method available for the determination of boron in water, air, and solid waste samples (APHA 1985c; EPA 1982, 1986a; NIOSH 1984). Calorimetric procedures are as sensitive and precise but are more labor intensive. Calorimetric 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 LePape 1987).

6.3.2 On-going Studies

Examination of the literature does not suggest that major efforts are underway for the development of better methods for the determination of boron. This is due to the difficulties inherent in determining boron and the fact that an emphasis has not been placed on developing such methods because the element is relatively nontoxic.

7. REGULATIONS AND ADVISORIES

Because of its potential to cause adverse health effects in exposed people, a number of regulations and guidelines have been established for boron and its compounds by various national and state agencies. These values are summarized in Table 7-l.

7. REGULATIONS AND ADVISORIES

TABLE 7-1. Regulations and Guidelines Applicable to Boron and Compounds

Agency	Description	Information	References
NATIONAL			
Regulations:			
a. Air:			
OSHA	PEL TWA		OSHA 1989
	Boron oxide		(29 CFR
	Total dust	10 mg/m³	1910.1000)
	Respirable fraction	5 mg/m³	Table Z-1-A
	Sodium tetraborates	10 mg/m³	
	Ceiling		
	Boron tribromide	10 mg/m³ (1 ppm)	
	Boron trifluoride	3 mg/m³ (1 ppm)	
b. Water:			
EPA OWRS	General permits under NPDES	Yes	40 CFR 122,
	Boron, total		Appendix D,
			Table IV
c. Food:			
FDA	Food additive-modified hop extract		
	Boron	310 ppm	21 CFR 172.560
d. Other:			
EPA OERR	Reportable quantity (proposed)		EPA 1989b
	Boron trichloride	100 lbs	
	Boron trifluoride	100 lbs	
	Extremely Hazardous Substance TPQ		EPA 1987a
	Boron trichloride	500 lbs	(40 CFR 355)
	Boron trifluoride	500 lbs	
EPA OPP	Tolerances for pesticide chemicals on raw agricultural commodities		
	Boron	8 to 30 ppm	40 CFR 180.271
Guidelines:			
a. Air:			
ACGIH	TLV TWA		ACGIH 1986
	Sodium tetraborates		
	Anhydrous and pentahydrate	1 mg/m³	
	Decahydrate	5 mg/m³	
	Boron oxide	10 mg/m³	
	Ceiling		
	Boron tribromide	1 ppm (10 mg/m³)	
	Boron trifluoride	1 ppm (3 mg/m³)	
NIOSH	IDLH		NIOSH 1985b
	Boron trifluoride	100 ppm	
b. Water:			
EPA OWRS	Ambient Water Quality Criteria		EPA 1986b
	Long-term irrigation on sensitive crops	750 µg/L	
c. Other:			
EPA	Oral RfD		IRIS 1989
	Boron and Borates	9E-2 mg/kg/day	

7. REGULATIONS AND ADVISORIES

TABLE 7-1 (Continued)

Agency	Description	Information	References
STATE			
Regulations and Guidelines:			
a. Air:	Acceptable ambient air concentrations		NATICH 1989
Connecticut	Sodium tetraborates	20 $\mu g/m^3$ (8 hr)	
		100 $\mu g/m^3$ (8 hr)	
	Boron oxide	200 $\mu g/m^3$ (8 hr)	
	Boron tribromide	200 $\mu g/m^3$ (8 hr)	
	Boron trifluoride	0 $\mu g/m^3$ (8 hr)	
Nevada	Sodium tetraborates	2.4E-2 mg/m^3 (8 hr)	
	Boron oxide	2.38E-1 mg/m^3 (8 hr)	
	Boron tribromide	2.38E-1 mg/m^3 (8 hr)	
	Boron trifluoride	7.1E-2 mg/m^3 (8 hr)	
North Dakota	Sodium tetraborates	1.0E-2 mg/m^3 (8 hr)	
		5.0E-2 mg/m^3 (8 hr)	
	Boron oxide	1.0E-2 mg/m^3 (8 hr)	
	Boron tribromide	1.0E-1 mg/m^3 (8 hr)	
	Boron trifluoride	3.0E-2 mg/m^3 (8 hr)	
Virginia	Sodium tetraborates	16 $\mu g/m^3$ (24 hr)	
	Boron oxide	160 $\mu g/m^3$ (24 hr)	
	Boron tribromide	80 $\mu g/m^3$ (24 hr)	
	Boron trifluoride	25 $\mu g/m^3$ (24 hr)	

ACGIH = American Conference of Governmental Industrial Hygienists; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; IDLH = Immediately Dangerous to Life or Health Level; NIOSH = National Institute for Occupational Safety and Health; NPDES = National Pollutant Discharge Elimination System; OERR = Office of Emergency and Remedial Response; OPP = Office of Pesticide Products; OSHA = Occupational Safety and Health Administration; OWRS = Office of Water Regulations and Standards; PEL = Permissible Exposure Limit; TLV = Threshold Limit Value; TPQ = Threshold Planning Quantity; TWA = Time-Weighted Average

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9. GLOSSARY

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

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 (K_d) -- The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

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.

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.

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.

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.

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

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.

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

9. GLOSSARY

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

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

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

In Vivo -- Occurring within the living organism.

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

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

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

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

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

Lowest-Observed-Adverse-Effect Level (LOAEL) -- The lowest dose 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.

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

Minimal Risk Level -- An estimate of daily human exposure to a chemical that is likely to be without an appreciable risk of deleterious effects (noncancerous) over a specified duration of exposure.

Mutagen -- A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

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

No-Observed-Adverse-Effect Level (NOAEL) -- The dose of 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.

Permissible Exposure Limit (PEL) -- An allowable exposure level in workplace air averaged over an g-hour shift.

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

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 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 CERCLA. Reportable quantities are: (1) 1 lb or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 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.

Short-Term Exposure Limit (STEL) -- The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

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

9. GLOSSARY

Teratogen -- A chemical that causes structural defects that affect the development of an organism,

Threshold Limit Value (TLV) -- A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

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

Toxic Dose (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.

Uncertainty Factor (UF) -- A factor used in operationally deriving the RfD 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 LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX A

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile *is* a health effects summary written in nontechnical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or substance 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 substance.

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

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-l and 2-2) are used to summarize health effects by duration of exposure and endpoint and to illustrate graphically levels of exposure associated with those effects. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed- Adverse-Effect Levels (LOAELS) for Less Serious and Serious health effects, or Cancer Effect Levels (CELs). In addition, these tables and figures illustrate differences in response by species, Minimal Risk Levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. The LSE tables and figures can be used 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.

The legends presented below demonstrate the application of these tables and figures. A representative example of LSE Table 2-l and Figure 2-l are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-l

1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data 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 Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-l) and oral (LSE Figure 2-2) routes.

2) Exposure Duration Three exposure periods: acute (14 days or less); intermediate (15 to 364 days); and chronic (365 days or more) are presented within each route of exposure. In this example, an inhalation study of intermediate duration exposure is reported.

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.

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 define a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in Figure 2-l).

5) Species The test species, whether animal or human, are identified in this column.

6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were expbsed to [substance x] via inhalation for 13 weeks, 5 days per week, for 6 hours per day.

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 sys terns. In the example of key number 18, one systemic effect (respiratory) was investigated in this study.

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

9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest exposure level 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 "Less Serious" respiratory effect reported in key number 18 (hyperplasia) occurred at a LOAEL of 10 ppm.

10) Reference The complete reference citation is given in Chapter 8 of the profile.

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

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

LEGEND

See LSE Figure 2-1

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

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

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

15) Levels of Exposure Exposure levels for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure levels are reported on the log scale "y" axis. Inhalation exposure is reported in mg/m3 or ppm and oral exposure is reported in mg/kg/day.

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

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

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18) Estimated UDDer-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 in10,000,000. These risk levels are derived from 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 2-1. Levels of Significant Exposure to [Chemical x] - Inhalation**

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

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

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

CEL = cancer effect level; d = day(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

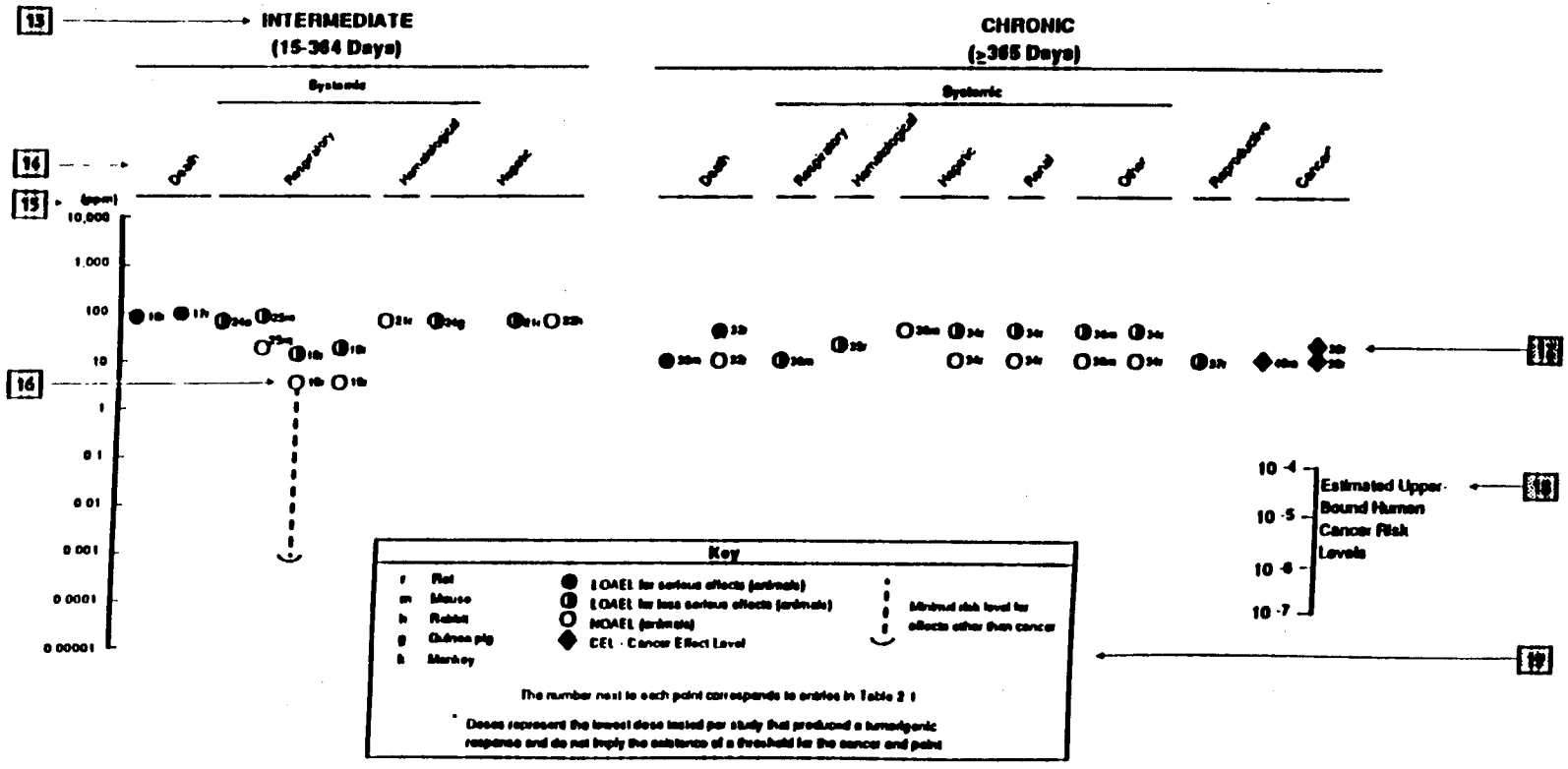

FIGURE 2-1. Levels of Significant Exposure to [Chemical X]-Inhalation

APPENDIX A

Chapter 2 (Section 2.4)

Relevance to Public Health

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicological, epidemiological, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?

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

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

The section discusses health effects by end point. Human data are presented first, then animal data. Both are organized by route of exposure (inhalation, oral, and dermal) and by duration (acute, intermediate, and chronic). In vitro data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

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

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

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information was available, MRLs were derived. MRLs are specific for route (inhalation or oral) and duration (acute, intermediate, or chronic) of exposure. Ideally, MRLs can be derived from all six exposure scenarios (e.g., Inhalation - acute, -intermediate, -chronic; Oral - acute, - intermediate, - chronic). These MRLs are not meant to support regulatory action, but to aquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a substance emission, given the concentration of a contaminant in air or the estimated daily dose received via food or water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

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MRL users should be familiar with the toxicological information on which the number is based. Section 2.4, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.6, "Interactions with Other Chemicals" and 2.7, "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 used by the Environmental Protection Agency (EPA) (Barnes and Dourson, 1988; EPA 1989a) to derive reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the end point which, in its best judgement, represents the most sensitive humanhealth 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 effects (e.g., systemic, neurological, and developmental). In order to compare NOAELs and LOAELs for specific end points, all inhalation exposure levels are adjusted for 24hr exposures and all intermittent exposures for inhalation and oral routes of intermediate and chronic duration are adjusted for continous exposure (i.e., 7 days/week). If the information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with-the highest NOAEL that does not exceed any adverse effect levels. The NOAEL is the most suitable end point for deriving an MRL. When a NOAEL is not available, a Less Serious LOAEL can be used to derive an MRL, and an uncertainty factor (UF) of 10 is employed. MRLs are not derived from Serious LOAELs. Additional uncertainty factors of 10 each are used 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 adjusted inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX B

ACRONYMS, ABBREVIATIONS, AND SYMBOLS USED IN TEXT

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
f_1	first generation
fpm	feet per minute
ft	foot
FR	Federal Register
g	gram
GC	gas chromatography
HPLC	high performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
Kd	adsorption ratio
kg	kilogram
Koc	octanol-soil partition coefficient
Kow	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{LO}	lethal concentration low
LC_{50}	lethal concentration 50 percent kill
LD_{LO}	lethal dose low
LD_{50}	lethal dose 50 percent kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter

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mg	milligram
min	minute
mL	milliliter
mm	millimeters
mmo1	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectroscopy
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
nm	nanometer
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportional mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
Rfd	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio
STEL	short-term exposure limit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxic Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
WHO	World Health Organization
>	greater than
≥	greater than or equal to

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=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micron
μg	microgram

APPENDIX C

PEER REVIEW

A peer review panel was assembled for boron. The panel consisted of the following members: Dr. Rajender Abraham, a private consultant; Dr. Hugh Evans, Associate Professor of Chemistry, Institute of Environmental Medicine, New York Unversity Medical Center; Dr. Ernest Foulkes, Director, Department of Environmental Health, University of Cincinnati; and Dr. William Buck, Professor of Toxicology, College of Veterinary Medicine, University of Illinois. These experts collectively have knowledge of boron's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. A second panel of reviewers was assembled to review the sections on mitigation of effects. This panel consisted of: Dr. Brent Burton, Medical Director, Oregon Poison Center, Oregon Health Sciences University, Portland, Oregon; Dr. Alan Hall, Private Consultant, Evergreen, Colorado; and Dr. Alan Woolf, Director of Clinical Pharmacology and Toxicology, Massachusetts Poison Control System, The Children's Hospital, Boston, Massachusetts. All reviewers were selected in conformity with the conditions for peer review specified in the Comprehensive Environmental'Response, Compensation, and Liability Act of 1986, Section 104.

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

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

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