# 2. RELEVANCE TO PUBLIC HEALTH

## 2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO BORON IN THE UNITED STATES

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

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

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

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

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

## 2.2 SUMMARY OF HEALTH EFFECTS

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

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

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

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

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

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

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

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

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

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

## 2.3 MINIMAL RISK LEVELS (MRLs)

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

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

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

***Inhalation MRLs***

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

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

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

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

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

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

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

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

***Oral MRLs***

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

### 2.3.1 Chronic-Duration Oral Studies

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