Boron and Compounds; CASRN 7440-42-8

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR BORON AND COMPOUNDS

File First On-Line 10/01/89

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	08/05/2004
Inhalation RfC (I.B.)	qualitative discussion	08/05/2004
Carcinogenicity Assessment (II.)	yes	08/05/2004

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Boron and Compounds
CASRN - 7440-42-8
Section I.A. Last Revised — 08/05/2004

In general, the oral Reference Dose (RfD) is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis and is expressed in units of mg/kg-day. Please refer to the guidance documents at http://www.epa.gov/iris/backgrd.html for an elaboration of these concepts. Since RfDs can be derived for the noncarcinogenic health effects of substances that are also

carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

This RfD replaces the previous RfD of 0.09 mg/kg-day entered on IRIS on 10/01/89 (see section VII. Revision History). Chronic toxicity in dogs (Weir and Fisher, 1972) was used previously to develop the RfD for boron. Recently, developmental data in three species (rats, mice, and rabbits) have become available. Based on the new developmental data and several limitations of the dog studies (Section I.A.1), decreased fetal body weight in rats is recommended as the critical effect for development of an RfD.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	RfD
Decreased fetal weight (developmental) **Rat dietary gestational exposure to boric acid** **Price et al., 1996a; Heindel et al., 1992**	$BMDL_{05}$: 10.3 mg/kg-day	66	2E-1 mg/kg-day

* Conversion Factors and Assumptions: Doses in mg boric acid were converted to mg boron by multiplying by the ratio of the formula weight of boron to the molecular weight of boric acid (10.81/61.84 = 0.1748). Similarly, doses in mg borax were converted to mg boron by multiplying by the ratio of the formula weight of boron to the molecular weight of borax (4 x 10.81/381.3 = 0.1134). The UF is data-derived and is based on variability and uncertainty in toxicokinetics and toxicodynamics.

The $BMDL_{05}$ was derived by Allen et al. (1996) using combined data from Price et al. (1996a) and Heindel et al. (1992). The BMR of a 5% decrease in fetal weight, relative to control, was selected for several reasons to help identify the point of departure. The dose response data (Price et al., 1996a) showed a statistically significant trend of decreasing fetal weights with increasing exposure to boron throughout the range of exposures tested. The exposure associated with the 5% weight decrease fell well within the range of the experimental data.

Although the responses at lower doses were also lower than control response, the data base for boron is mixed concerning whether decreased fetal weights indicate a transient or more permanent functional alteration. For example, decreased weights did not persist in the companion study (Phase II of Price et al., 1996a, 1994). Therefore, no further adjustments were considered for identifying a level of oral exposure to boron associated with minimal level of risk.

I.A.2. Principal and Supporting Studies (Oral RfD)

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

Price, CJ; Strong, PL; Marr, MC; Myers, CB; Murray, FJ. (1996a.) Developmental toxicity NOAEL and postnatal recovery in rats fed boric acid during gestation. Fund Appl Toxicol 32:179-193.

Developmental (decreased fetal weights) effects are considered the critical effect. The basis for calculating the RfD is the $BMDL_{05}$ of 10.3 mg boron/kg-day calculated from the developmental effects reported by Heindel et al. (1992) and Price et al. (1996a).

Heindel et al. (1992) and Price et al. (1990) treated timed-mated Sprague-Dawley rats (29/group) with a diet containing 0, 0.1, 0.2, or 0.4% boric acid from gestation day (gd) 0-20. The investigators estimated that the diet provided 0, 78, 163, or 330 mg boric acid/kg-day (0, 13.6, 28.5 or 57.7 mg B/kg-day). Additional groups of 14 rats each received boric acid at 0 or 0.8% in the diet (539 mg/kg-day or 94.2 mg B/kg-day) on gd 6-15 only. Exposure to 0.8% was limited to the period of major organogenesis in order to reduce the preimplantation loss and early embryolethality indicated by the range-finding study and, hence, provide more opportunity for teratogenesis. (The range-finding study found that exposure to 0.8% on gd 0-20 resulted in a decreased pregnancy rate [75% as compared with 87.5% in controls] and in greatly increased resorption rate per litter [76% as compared with 7% in controls]). Food and water intake, and body weights, as well as clinical signs of toxicity, were monitored throughout pregnancy. On gd 20, the animals were sacrificed and the liver, kidneys, and intact uteri were weighed, and corpora lutea were counted. Maternal kidneys, selected randomly (10 dams/group), were processed for microscopic evaluation. Live fetuses were dissected from the uterus, weighed, and examined for external, visceral, and skeletal malformations. Statistical significance was established at $p<0.05$. There was no maternal mortality during treatment. Food intake increased 5-7% relative to that of controls on gd 12-20 at 0.2 and 0.4%; water intake was not significantly altered by administration of boric acid (data not shown). At 0.8%, water and food intake decreased on days 6-9 and increased on days 15-18, relative to controls. Pregnancy rates ranged between 90 and 100% for all groups of rats and appeared unrelated to

treatment. Maternal effects attributed to treatment included a significant and dose-related increase in relative liver and kidney weights at 0.2% or more, a significant increase in absolute kidney weight at 0.8%, and a significant decrease in body-weight gain during treatment at 0.4% or more. Corrected body weight gain (gestational weight gain minus gravid uterine weight) was unaffected except for a significant increase at 0.4%. Examination of maternal kidney sections revealed minimal nephropathy in a few rats (unspecified number), but neither the incidence nor the severity of the changes was dose related.

Treatment with 0.8% boric acid (gd 6-15) significantly increased prenatal mortality; this was due to increases in the percentage of resorptions per litter and percentage of late fetal deaths per litter. The number of live fetuses per litter was also significantly decreased at 0.8%. Average fetal body weight (all fetuses or male or female fetuses) per litter was significantly reduced in all treated groups versus controls in a dose-related manner. Mean fetal weights were 94, 87, 63, and 46% of the corresponding control means for the 0.1, 0.2, 0.4 and 0.8% dose groups, respectively. The percentage of malformed fetuses per litter and the percentage of litters with at least one malformed fetus were significantly increased at 0.2% or more. Treatment with 0.2% or more boric acid also increased the incidence of litters with one or more fetuses with a skeletal malformation. The incidence of litters with one or more pups with a visceral or gross malformation was increased at 0.4 and 0.8%, respectively. The malformations consisted primarily of anomalies of the eyes, the central nervous system, the cardiovascular system, and the axial skeleton. In the 0.4 and 0.8% groups, the most common malformations were enlarged lateral ventricles of the brain and agenesis or shortening of rib XIII. The percentage of fetuses with variations per litter was reduced relative to controls in the 0.1 and 0.2% dosage groups (due primarily to a reduction in the incidence of rudimentary or full ribs at lumbar I), but was significantly increased in the 0.8% group. The variation with the highest incidence among fetuses was wavy ribs. Based on the changes in organ weights, a maternal lowest-observed-adverse-effect level (LOAEL) of 0.2% boric acid in the feed (28.5 mg B/kg-day) can be established; the maternal no-observed-adverse-effect level (NOAEL) is 0.1% or 13.6 mg B/kg-day. Based on the decrease in fetal body weight per litter, the level of 0.1% boric acid in the feed (13.6 mg B/kg-day) is a LOAEL; a NOAEL was not defined.

In a follow-up study, Price et al. (1996a, 1994) administered boric acid in the diet (at 0, 0.025, 0.050, 0.075, 0.100, or 0.200%) to timed-mated CD rats, 60 per group, from gd 0-20. Throughout gestation, rats were monitored for body weight, clinical condition, and food and water intake. This experiment was conducted in two phases, and in both phases offspring were evaluated for post-implantation mortality, body weight and morphology (external, visceral, and skeletal). Phase I of this experiment was considered the teratology evaluation and was terminated on gd 20 when uterine contents were evaluated. The calculated average dose of boric acid consumed for Phase l dams was 19, 36, 55, 76, and 143 mg/kg-day (3.3, 6.3, 9.6, 13.3, and 25 mg B/kg-day). During Phase I, no maternal deaths occurred and no clinical

symptoms were associated with boric acid exposure. Maternal body weights did not differ among groups during gestation, but statistically significant trend tests associated with decreased maternal body weight (gd 19 and 20 at sacrifice) and decreased maternal body weight gain (gd 15-18 and gd 0-20) were indicated. In the high-dose group, there was a 10% reduction (statistically significant in the trend test $p<0.05$) in gravid uterine weight when compared with controls. The authors indicated that the decreasing trend of maternal body weight and weight gain during late gestation reflected reduced gravid uterine weight. Corrected maternal weight gain (maternal gestational weight gain minus gravid uterine weight) was not affected. Maternal food intake was only minimally affected at the highest dose and only during the first 3 days of dosing. Water intake was higher in the exposed groups after gd 15. The number of ovarian corpora lutea and uterine implantation sites, and the percent preimplantation loss were not affected by boric acid exposure.

Offspring body weights were significantly decreased in the 13.3 and 25 mg B/kg-day dose groups on gd 20. The body weight of the low- to high-dose groups, respectively, were 99, 98, 97, 94, and 88% of control weight. There was no evidence of a treatment-related increase in the incidence of external or visceral malformations or variations when considered collectively or individually. On gd 20, skeletal malformations or variations considered collectively showed a significant increased percentage of fetuses with skeletal malformations per litter. Taken individually, dose-related response increases were observed for short rib XIII, considered a malformation in this study, and wavy rib or wavy rib cartilage, considered a variation. Statistical analyses indicated that the incidence of short rib XIII and wavy rib were both increased in the 13.3 and 25 mg B/kg-day dose groups relative to controls. A significant trend test ($p<0.05$) was found for decrease in rudimentary extra rib on lumbar I, classified as a variation. Only the high-dose group had a biologically relevant, but not statistically significant, decrease in this variation. The LOAEL for Phase I of this study was considered to be 0.1% boric acid (13.3 mg B/kg-day) based on decreased fetal body weight. The NOAEL for Phase I of this study was considered to be 0.075% boric acid (9.6 mg B/kg-day).

In Phase II, dams were allowed to deliver and rear their litters until postnatal day (pnd) 21. The calculated average doses of boric acid consumed for Phase II dams were 19, 37, 56, 74, and 145 mg/kg-day (3.2, 6.5, 9.7, 12.9, and 25.3 mg B/kg-day). This phase allowed a follow-up period to determine whether the incidence of skeletal defects in control and exposed pups changed during the first 21 postnatal days. Among live born pups, there was a significant trend test for increased number and percent of dead pups between pnd 0 and 4, but not between pnd 4 and 21; this appeared to be due to an increase in early postnatal mortality in the high dose, which did not differ significantly from controls and was within the range of control values for other studies in this laboratory. On pnd 0, the start of Phase II, there were no effects of boric acid on the body weight of offspring (102, 101, 99, 101, and 100% of controls, respectively). There were also no differences through termination on pnd 21; therefore, fetal body weight

deficits did not continue into this postnatal period (Phase II). The percentage of pups per litter with short rib XIII was still elevated on pnd 21 in the 0.20% boric acid dose group (25.3 mg B/kg-day), but there was no incidence of wavy rib, and none of the treated or control pups on pnd 21 had an extra rib on lumbar 1. The NOAEL and LOAEL for phase II of this study were 12.9 and 25.3 mg B/kg-day, respectively.

The Institute for Evaluating Health Risks (IEHR, 1997) concluded that there was a consistent correlation between boric acid exposure and the different effects on rib and vertebral development in rats, mice, and rabbits (see the Additional Studies section for effects in mice and rabbits). Of these three species, the rat was the most sensitive to low-dose effects. A causal association between exposure to boric acid and the short rib XIII existed when fetuses were examined at late gestation or when pups where examined at pnd 21. The IEHR (1997) concluded that decreased fetal body weight occurred at the same dose or at doses lower than those at which skeletal changes were observed and that this was the preferred data set for deriving quantitative estimates.

Several benchmark dose (BMD) analyses were conducted (Allen et al., 1996) using all relevant endpoints to analyze data from Heindel et al. (1992) and Price et al. (1996a, 1994) studies alone and combined data from the two studies. Changes in fetal weight were analyzed by taking the average fetal weight for each litter with live fetuses. Those averages were considered to represent variations in a continuous variable. A BMD was defined in terms of a prespecified level of effect, referred to as the benchmark response (BMR) level (Kavlock et al., 1995). For mean fetal weight analysis, the BMR was a 5% decrease in the mean fetal weight relative to control. The $BMDL_{05}$ was defined as the 95% lower bound on the dose corresponding to the BMR. A continuous power model was used. Goodness of fit was evaluated using F-tests that compared the lack of model fit to an estimate of pure error.

For all endpoints, the results of the Heindel et al. (1992) and Price et al. (1994, 1996a) studies were compared. The dose-response patterns were examined to determine if a single function could adequately describe the responses in both studies. This determination was based on a likelihood ratio test. The maximum log-likelihoods from the models fit to the two studies considered separately were added together; the maximum log-likelihood for the model fit to the combined results was then subtracted from this sum. Twice that difference is distributed approximately as a chi-square random variable (Cox and Lindley, 1974). The degrees of freedom for that chi-square random variable are equal to the number of parameters in the model plus 1. The additional degree of freedom was available because the two control groups were treated as one group in the combined results, which eliminates the need to estimate one of the intra-litter correlation coefficients (for beta-binomial random variables) or variances (for normal random variables) that was estimated when the studies were treated separately. The critical values from the appropriate chi-square distributions (associated with a p-value of

0.01) were compared to the calculated values. When the calculated value was less than the corresponding critical value, the combined results were used to estimate BMDLs; this result indicated that the responses from the two studies were consistent with a single dose-response function. $BMDL_{05}$ values calculated with a continuous power model for fetal body weight (litter weight averages) were less than those for all other relevant endpoints. The $BMDL_{05}$ based on the combined results of the two studies was 10.3 mg B/kg-day, which was very close to the NOAEL of 9.6 mg B/kg-day from the Price et al. (1996a, 1994) study.

In addition to the rat studies, the developmental effects of boric acid were also studied in mice and rabbits. Heindel et al. (1994, 1992) and Field et al. (1989) identified a NOAEL and LOAEL of 43.3 and 79 mg B/kg-day, respectively, for decreased fetal body weight in mice exposed to boric acid in the feed. Increased resorptions and malformations, especially short rib XIII, were noted at higher doses. Price et al. (1996b, 1991) and Heindel et al. (1994) identified a NOAEL and LOAEL of 21.9 and 43.7 mg B/kg-day for developmental effects in rabbits. Frank effects were found at the LOAEL, including high prenatal mortality and increased incidence of malformations, especially cardiovascular defects.

I.A.3. Uncertainty Factors (Oral RfD)

UF = 66

The animal-to-human and sensitive-human uncertainty factors (UF_A and UF_H) are each split into toxicokinetic (TK) and toxicodynamic (TD) components to apply existing rat and human toxicokinetic data to reduce the uncertainty in the boron RfD. The default values for the toxicokinetic and toxicodynamic components of both UF_A and UF_H are set at one-half order of magnitude ($10^{0.5}$), or 3.16, each.

The revised formula for calculating the RfD with UF_A and UF_H split into TK and TD factors is given as:

$$RfD = \frac{D_c}{(AF_{AK} \times AF_{AD} \times AF_{HK} \times AF_{HD} \times UF)}$$

where:

- D_C is the "critical" dose (NOAEL, LOAEL, BMD) defined in the critical study(ies)
- AF_{AK} is the interspecies toxicokinetic adjustment factor (default = 3.16)

- AF_{AD} is the interspecies toxicodynamic adjustment factor (default = 3.16)
- AF_{HK} is the interindividual toxicokinetic adjustment factor (default = 3.16)
- AF_{HD} is the interindividual toxicodynamic adjustment factor (default = 3.16)
- UF is the aggregate uncertainty factor

The product of AF_{AK} and AF_{AD} replaces the animal-to-human (interspecies) uncertainty factor (UF_A) in the standard RfD methodology. Similarly, the product of AF_{HK} and AF_{HD} replaces the sensitive human (interindividual variability) uncertainty factor (UF_H). Each of the adjustment factors is the product of data-derived scaling factors and residual uncertainty. The aggregate uncertainty factor (UF) is equal to the product of all other uncertainty factors: subchronic-to-chronic (UF_S), LOAEL-to-NOAEL (UF_L), and data base adequacy (UF_D). The product of all the terms in the denominator is given the term, "Total Adjustment Factor," and is designated as AF_{TOT}. The formula is described in more detail in Section 5.1.3 in the Toxicological Review.

Although the toxic effects of boron are manifested in the offspring, pregnant females (for both humans and test animals) are considered to be the "sensitive" population with respect to establishing an equivalent toxic dose across species. Given the near-first order kinetics of boron, maternal toxicokinetic variability is likely to be an adequate surrogate for the fetal dose variability. As boron is not metabolized and almost entirely eliminated in the urine, clearance of boron by the kidney can be used as the key toxicokinetic factor, with a consideration of the relative volumes of distribution between rats and humans.

As there is an assumption of relatively constant intake of boron, and the toxic outcome is most likely related to a continuous exposure over an extended period during fetal development, the most appropriate estimator for internal dose is the average steady-state circulating boron concentration. Because boron distributes primarily to total body water and bone, a two-compartment steady-state kinetic model is used to relate internal circulating boron concentration to external exposure (see Section 5.1.3 in the Toxicological Review for details). The resulting formula for calculating the interspecies adjustment factor (AF_{AK}) is given by:

$$AF_{AK} = \frac{Cl_r \times f_{ah} \times BW_h}{Cl_h \times f_{ar} \times BW_r}$$

where:

- *Cl* is the clearance rate (ml/min)

- f_a is the fraction of ingested boron absorbed into the body from the gut
- BW is body weight (kg)

The trailing subscript designates the species ® = rat, h = human). The mean boron clearance for pregnant rats and pregnant women was 1.00 and 66.1 ml/min, respectively, determined from the kinetic studies of U.S. Borax (2000), Vaziri et al. (2001), and Pahl et al. (2001). The mean body weights for pregnant rats and pregnant women from those studies are 0.303 and 67.6 kg, respectively. The absorption fractions, f_{ah} and f_{ar}, are set to 0.92 (Schou et al., 1984) and 0.95 (Vanderpool et al., 1994), respectively. The resulting AF_{AK} is 3.3.

For the assessment of interindividual toxicokinetic variability, glomerular filtration rate (GFR) is used as a surrogate for boron clearance. The population of particular interest is pregnant women, reflecting the critical effect of decreased fetal weight. Emphasis is placed on considering risks to pregnant women with compromised renal function, such as the approximately 3-5 percent of women who suffer from preeclampsia during pregnancy. Interindividual variability among pregnant women was assessed in two ways: using GFR data from a small group of preeclamptic women in the third trimester and by a modification of Dourson et al. (1998) related to GFR in normal pregnancies. The basic formula modified from Dourson et al. (1998) for AF_{HK} is:

$$AF_{HK} = \quad GFR_{AVG}$$

$$GFR_{AVG} - 3SD_{GFR}$$

where GFR_{AVG} and SD_{GFR} are the mean and standard deviation of the GFR (ml/min) for the general healthy population of pregnant women. The use of three standard deviations rather than two (as in Dourson et al., 1998) is based on obtaining adequate coverage of pregnant women with very low GFR (see Section 5.1.3 in the Toxicological Review). AF_{HK} is determined from the average AF_{HK} of 1.93 from three separate studies (Dunlop, 1981; Krutzén et al., 1992; Sturgiss et al., 1996). This value was rounded up from 1.93 to 2.0 to account for uncertainties which may not be addressed by reliance on these studies of GFR and its natural variability among humans. The data on preeclamptic women presented by Krutzén et al. (1992) were considered insufficient to base the interindividual AF_{HK} factor. Use of the mean (128 ml/min) and standard deviation (33 ml/min) in this sensitive subgroup of preeclamptic women likely overestimates the spread of GFR values below the mean due to the likelihood of a lognormal distribution of GFR values, and the contribution of measurement variability (beyond biological variability) to the statistical confidence limits. Given these considerations, the ~2-fold interindividual variability factor derived from three standard deviations below the

mean of three studies for pregnancy GFR (mean = 161.5 ml/min; mean - 3 SD = 85.8) is considered preferable for providing adequate coverage to women predisposed to adverse birth outcomes due to renal complications.

As there are no toxicodynamic data sufficient to warrant the replacement of the default values for either UF_A or UF_H for boron, AF_{AD} and AF_{HD} are each assigned the default value of 3.16. The overall adjustment factor (AF_{TOT}) is 66 (3.3 x 3.16 x 2 x 3.16).

I.A.4. Additional Studies/Comments (Oral RfD)

The subchronic and chronic toxicity of borax and boric acid was studied in dogs administered these compounds in the diet (Weir and Fisher, 1972; U.S. Borax Research Corp., 1963, 1966, 1967). In the supporting subchronic study, groups of beagle dogs (5/sex/dose/compound) were administered borax (sodium tetraborate decahydrate) or boric acid for 90 days at dietary levels of 17.5, 175, and 1750 ppm boron (male: 0.33, 3.9, and 30.4 mg B/kg-day; female: 0.24, 2.5, and 21.8 mg B/kg-day) and compared with an untreated control group of 5 dogs/sex (Weir and Fisher, 1972; U.S. Borax Research Corp., 1963). A high-dose male dog died as a result of complications of diarrhea on day 68 of the study with severe congestion of the mucosa of the small and large intestines and congestion of the kidneys. No clinical signs of toxicity were evident in the other dogs. The testes were the primary target of boron toxicity. At the high dose, mean testes weight was decreased 44% in males fed borax (9.6g) and 39% in males fed boric acid (10.5 g) compared with controls (17.2 g). Also at this dose, mean testes:body weight ratio (control: 0.2%; borax: 0.1%; boric acid: 0.12%) and mean testes:brain weight ratio (control: 22%; borax: 12%) were significantly reduced. Decreased testes:body weight ratio was also observed in one dog from the mid-dose boric acid group. Microscopic pathology revealed severe testicular atrophy in all high-dose male dogs, with complete degeneration of the spermatogenic epithelium in most cases. No testicular lesions were found in the lower dose groups. Hematological effects were also observed in high-dose dogs. Decreases were found for both hematocrit (15 and 6% for males and females, respectively) and hemoglobin (11% for both males and females) at study termination in borax-treated dogs. Pathological examination revealed accumulation of hemosiderin pigment in the liver, spleen and kidney, indicating breakdown of red blood cells, in males and females treated with borax or boric acid. Other effects in high-dose dogs were decreased thyroid:body weight ratio (control: 0.009%; borax: 0.006%; boric acid: 0.006%) and thyroid:brain weight ratio (control: 0.95%; borax: 0.73%) in males; also at the high dose were increases in brain:body weight ratio (borax) and liver:body weight ratios (boric acid) in females and a somewhat increased proportion of solid epithelial nests and minute follicles in the thyroid gland of borax-treated males, lymphoid infiltration and atrophy of the thyroid in boric-acid treated females, and increased width of the zona reticularis (borax males and females, boric acid females) and zona glomerulosa (boric acid females) in the adrenal gland. This study identified a LOAEL for

systemic toxicity in dogs of 1750 ppm boron (male: 30.4 mg B/kg-day; female: 21.8 mg B/kg-day) and a NOAEL of 175 ppm boron (male: 3.9 mg B/kg-day; female: 2.5 mg B/kg-day) following subchronic exposure.

In the chronic toxicity study, groups of beagle dogs (4/sex/dose/compound) were administered borax or boric acid by dietary admix at concentrations of 0, 58, 117, and 350 ppm boron (0, 1.4, 2.9, and 8.8 mg B/kg-day) for 104 weeks (Weir and Fisher, 1972; U.S. Borax Research Corp., 1966). There was a 52-week interim sacrifice and a 13-week "recovery" period after 104 weeks on test article for some dogs. Control animals (4 male dogs) served as controls for the borax and boric acid dosed animals. One male control dog was sacrificed after 52 weeks, two male control dogs were sacrificed after 104 weeks, and one was sacrificed after the 13-week recovery period with 104 weeks of treatment. The one male control dog sacrificed after the 13-week recovery period demonstrated testicular atrophy. Sperm samples used for counts and motility testing were taken only on the control and high dosed male dogs prior to the 2-year sacrifice. At a dose level of 8.8 mg B/kg-day in the form of boric acid, one dog sacrificed at 104 weeks had testicular atrophy. Two semen evaluations (taken after 24 months treatment) were performed on dogs treated at the highest dose (8.8 mg B/kg-day). Two of two borax-treated animals had samples that were azoospermic and had no motility while one of two boric acid treated animals had samples that were azoospermic. The authors reported that there did not appear to be any definitive test article effect on any parameter examined. The study pathologist considered the histopathological findings as being "not compound-induced." Tumors were not reported.

In a follow-up to this study, groups of beagle dogs (4/sex/dose/compound) were given borax or boric acid in the diet at concentrations of 0 and 1170 ppm boron (0 and 29.2 mg B/kg-day) for up to 38 weeks (Weir and Fisher, 1972; U.S. Borax Research Corp., 1967). New control dogs (4 males) were used for this follow up study. Two were sacrificed at 26 weeks and two at 38 weeks. At the 26-week sacrifice, one of two had spermatogenesis and (5%) atrophy. One was reported normal. At 38 weeks, one had decreased spermatogenesis, and the other had testicular atrophy. The test animals were noted throughout the study to have about an 11% decrease in the rate of weight gain when compared with control animals. Interim sacrifice of two animals from each group at 26 weeks revealed severe testicular atrophy and spermatogenic arrest in male dogs treated with either boron compound. Testes weight, testes:body weight ratio and testes:brain weight ratios were all decreased. Effects on other organs were not observed. Exposure was stopped at 38 weeks; at this time, one animal from each group was sacrificed and the remaining animal from each group was placed on the control diet for a 25-day recovery period prior to sacrifice. After the 25-day recovery period, testes weight and testes weight:body weight ratio were similar to controls in both boron-treated males, and microscopic examination revealed the presence of moderately active spermatogenic epithelium in one of these dogs. The researchers suggested that this finding,

although based on a single animal, indicates that boron-induced testicular degeneration in dogs may be reversible upon cessation of exposure. When the 2-year and 38-week dog studies are considered together, an overall NOAEL and LOAEL for systemic toxicity can be established at 8.8 and 29.2 mg B/kg-day, respectively, based on testicular atrophy and spermatogenic arrest.

These dog studies were previously used to calculate the RfD for boron (IRIS 10/01/1989; see Section VII. Revision History). Based on newer developmental data in rats and several limitations in the dog studies, the critical effect is now considered to be decreased fetal body weight in rats. Some limitations of the dog studies include (1) the small number of test animals per dose group (n=4), (2) the use of shared control animals in the borax and boric acid studies so that at most two control animals were sacrificed at any time period, (3) the observation of testicular damage in three of four control animals, and (4) the NOAEL and LOAEL were taken from two different studies of different duration. Also, the study pathologist considered the histopathological findings as being "not compound-induced." Based on the small number of animals and the wide range of background variability among the controls, these studies do not appear to be appropriate at this time for establishment of an RfD.

Reproductive and systemic toxicity studies have identified the testes as a sensitive target of boron toxicity in rats and mice, although at higher doses than in the dog study (Weir and Fisher, 1972; Seal and Weeth, 1980; NTP, 1987; Fail et al., 1991). The testicular effects included reduced organ weight and organ:body weight ratio, atrophy, degeneration of the spermatogenic epithelium, impaired spermatogenesis, reduced fertility, and sterility (Weir and Fisher, 1972; Seal and Weeth, 1980; NTP, 1987; Fail et al., 1991; Dixon et al., 1979; Linder et al., 1990; Treinen and Chapin, 1991; Ku et al., 1993).

Boron is a trace element for which essentiality is suspected but has not been directly proven in humans (Nielsen, 1991, 1992, 1994; NRC, 1989; Hunt, 1994; Mertz, 1993). Because deficiency in humans has not been established, there are no adequate data from which to estimate a human requirement, and no provisional allowance has been established (NRC, 1989). However, boron deprivation experiments with animals and three human clinical studies have yielded some persuasive findings for the hypothesis that boron is nutritionally essential as evidenced by the demonstration that it affects macromineral and cellular metabolism at the membrane level (Nielsen, 1994). A close interaction between boron and calcium has been suggested. This interaction appears to affect similar systems that indirectly influence many variables including modification of hormone action and alteration of cell membrane characteristics (Nielsen et al., 1987; Nielsen, 1991, 1992, 1994). Data from three human studies of potential boron essentiality show that dietary boron can affect bone, brain, and kidney variables. The subjects in most of these studies, however, were under some form of nutritional or metabolic stress affecting calcium metabolism, including reduced intake of

magnesium or physiologic states associated with increased loss of calcium from bone or the body (e.g., postmenopausal women).

Based on the studies in which most subjects who consumed 0.25 mg B/day responded to boron supplementation, Nielsen (1991) concluded that the basal requirement for boron is likely to be greater than 0.25 mg/day. Limited survey data indicate that the average dietary intake of boron by humans is 0.5-3.1 mg/day (7-44 µg/kg-day) (Nielsen, 1991). Boron has been known since the 1920s to be an essential micronutrient for the growth of all plants. The average U.S. adult male dietary intake of 1.52 ± 0.38 mg B/day (mean ± standard deviation) (Iyengar et al., 1988) was determined by U.S. Food and Drug Administration (FDA) total diet study methods. In a more recent study, Anderson et al. (1994) reported an intake of 1.21 ± 0.07 mg B/day for an average diet for 25- to 30-year-old males, as determined by FDA total diet study analyses. Similarly, the average dietary boron intake in Canada is reported to be 1.33 ± 0.13 mg B/day for women (Clarke and Gibson, 1988). Dietary boron consumption in Europe can be higher due to wine consumption (ECETOC, 1994). These and other investigators (Nielsen, 1992) also recognized that greater consumption of fruits, vegetables, nuts, and legumes (e.g., vegetarian diets) could raise dietary boron intake.

The Institute of Medicine (IOM, 2002) considered the essentiality of boron and have yet to establish a clear biological function for boron. They looked at human toxic doses citing Culver and Hubbard (1996) (see Toxicological Review Section 4.1.1) who reported no adverse effects at chronic doses of 2.5 mg/kg-day boric tartrate (approximately 1g of boric acid). IOM (2002) also cited Litovitz et al. (1988) where minimal to no toxicity was found at high doses of boron in 784 cases of boric acid ingestion. Nine infant cases were also cited by IOM (2002) where increased sensitivity of response was not noted in chronic exposure to boron compounds. Tolerable Intake Limits (UL) (see Toxicological Review Section 5.1.3) were set for pregnant women at 17 mg B/day for 14-18 years of age (using 57 kg as a median body weight for females of this age group). The UL for pregnant women at 19-50 years was set at 20 mg B/day (using 61 kg as the reference body weight for this age group).

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).

I.A.5. Confidence in the Oral RfD

Study — High
Database — High
RfD — High

Confidence in the principal developmental studies is high; they are well-designed studies that examined relevant developmental endpoints using a large number of animals. Confidence in the data base is high due to the existence of numerous studies, including several subchronic studies; chronic feeding studies in dogs, rats, and mice; a multigeneration study in rats; a continuous breeding reproductive study in mice; and developmental studies in rats, mice, and rabbits. High confidence in the RfD follows.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

I.A.6. EPA Documentation and Review of the Oral RfD

Source Document — U.S. EPA (2004)

This assessment was peer reviewed by a group of external scientists. Comments from the peer reviewers were evaluated carefully and considered by the Agency during the finalization of this assessment. A record of these comments is included in Appendix A of the Toxicological Review of Boron and Compounds (U.S. EPA, 2004). ***To review this appendix, exit to the toxicological review, Appendix A, External Peer Review -- Summary of Comments and Disposition (PDF)***

Agency Completion Date — 05/26/2004

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (fax), or hotline.iris@epa.gov (email address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Boron and Compounds
CASRN — 7440-42-8
Section I.B. Last Revised — 08/05/2004

In general, the Reference Concentration (RfC) is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfC considers toxic effects for both the respiratory system

(portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). The inhalation RfC (generally expressed in units of mg/m3) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis.

Inhalation RfCs are derived according to the *Interim Methods for Development of Inhalation Reference Doses* (U.S. EPA, 1989) and subsequently, according to *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994). Since RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.B.1. Inhalation RfC Summary

An RfC for boron is not recommended at this time. The literature regarding toxicity of boron by inhalation exposure is sparse. There is a report from the Russian literature of reduced sperm count and sperm motility from semen analysis of six workers who were a part of a group of male workers (n=28) exposed to very high concentrations of boron aerosols (22-80 mg/m^3) for over 10 years (Tarasenko et al., 1972). These effects are consistent with the testicular effects reported in oral studies, but have not been confirmed by other inhalation studies. Data from Tarasenko et al. (1972) are of limited value for risk assessment due to sparse details and small sample size. No effect on fertility was found in a much larger study of U.S. borate production workers (Whorton et al., 1994a,b, 1992), but exposure concentrations were much lower (approximately 2.23 mg/m^3 sodium borate or 0.31 mg B/m^3) in this study.

No target organ effects were found in the lone animal study, in which rats were exposed to 77 mg/m^3 of boron oxide aerosols (24 mg B/m^3) for 24 weeks, but testicular effects were examined only by limited histopathology (Wilding et al., 1959). This study also included a high dose group exposed to 470 mg/m^3 boron oxide (146 mg B/m^3) for 10 weeks, a concentration at which the aerosol formed a dense cloud of fine particles and covered the animals with dust. Systemic endpoints were not examined, but growth was reduced, and there was evidence of nasal irritation. Acute irritant effects are well documented in human workers exposed to borates, primarily at concentrations greater than 4.4 mg/m^3 (Wegman et al., 1994; Garabrant et al., 1984, 1985). However, there is no evidence for reduced pulmonary function in workers with prolonged exposure (Wegman et al., 1994).

These data are inadequate to support derivation of an RfC for boron because the data available do not include a well-conducted study that adequately evaluated the respiratory tract and no NOAEL or LOAEL could be established.

I.B.2. Principal and Supporting Studies (Inhalation RfC)

Not Applicable

I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

Not Applicable

I.B.4. Additional Studies/Comments (Inhalation RfC)

Not Applicable

I.B.5. Confidence in the Inhalation RfC

Not Applicable

I.B.6. EPA Documentation and Review of the Inhalation RfC

Source Document — U.S. EPA (2004)

This assessment was peer reviewed by a group of external scientists. Comments from the peer reviewers were evaluated carefully and considered by the Agency during the finalization of this assessment. A record of these comments is included in Appendix A of the Toxicological Review of Boron and Compounds (U.S. EPA, 2004). ***To review this appendix, exit to the toxicological review, Appendix A, External Peer Review -- Summary of Comments and Disposition (PDF)***

Agency Completion Date - 05/26/2004

I.B.7. EPA Contacts (Inhalation RfC)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (fax), or hotline.iris@epa.gov (email address).

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Boron and Compounds
CASRN — 7440-42-8
Last Revised — 08/05/2004

This section provides information on three aspects of the carcinogenic assessment for the substance in question: the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral and inhalation exposure. Users are referred to Section I of this file for information on long-term toxic effects other than carcinogenicity.

The rationale and methods used to develop the carcinogenicity information in IRIS is described in the *Draft Revised Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1999). The quantitative risk estimates are derived from the application of a low-dose extrapolation procedure, and both the central and upper bound estimates of risk per unit of exposure are presented. The quantitative risk estimates are presented in three ways (see Section II.B.1.) to better facilitate their use: (1) generally, the "oral slope factor" is the 95% upper bound on the estimate of risk per mg/kg-day of oral exposure; (2) the "drinking water unit risk" is the 95% upper bound on the estimate of risk, either per µg/L drinking water or per $\mu g/m^3$ air breathed; and (3) the 95% lower bound and central estimate on the estimated concentration of the chemical substance in drinking water or air when associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Under the *Draft Revised Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1999), data are inadequate for an assessment of human carcinogenic potential for boron. This characterization is based on the following summary of available evidence. No data were located regarding the existence of an association between cancer and boron exposure in humans. Studies available in animals were inadequate to ascertain whether boron causes cancer. The chronic rat feeding study conducted by Weir and Fisher (1972) was not designed as a cancer bioassay. Only a limited number of tissues were examined histopathologically, and the report failed to even mention tumor findings. The chronic mouse study conducted by NTP (1987) was adequately designed, but the results are difficult to interpret. There was an increase in hepatocellular carcinomas in low dose, but not high dose, male mice that was within the range of historical controls. The increase was statistically significant using the life table test, but not the incidental tumor test. The latter test is more appropriate when the tumor in question

is not the cause of death, as appeared to be the case for this study. There was also a significant increase in the incidence of subcutaneous tumors in low dose male mice. However, once again the increase was within the range of historical controls and was not seen in the high dose group. Low survival in both the low and high dose male groups (60 and 44%, respectively) may have reduced the sensitivity of this study for evaluation of carcinogenicity. The chronic mouse study conducted by Schroeder and Mitchener (1975) was inadequate to detect carcinogenicity because only one, very low dose level was used (0.95 mg B/kg-day) and the MTD was not reached. No inhalation cancer studies were located. Studies of boron compounds for genotoxicity were overwhelmingly negative, including studies in bacteria, mammalian cells and mice *in vivo*. Therefore, no quantitative assessment of carcinogenic potential via any route is possible.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).

II.A.2. Human Carcinogenicity Data

Not Available

II.A.3. Animal Carcinogenicity Data

Inadequate.

Weir and Fisher (1972) fed Sprague-Dawley rats a diet containing 0, 117, 35, or 1170 ppm boron as borax or boric acid for 2 years (approximately 0, 5.9, 17.5, or 58.5 mg B/kg-day). There were 70 rats/sex in the control groups and 35/sex in the groups fed boron compounds. At 1170 ppm, rats receiving both boron compounds had decreased food consumption during the first 13 weeks of study and suppressed growth throughout the study. Signs of toxicity at this exposure level included swelling and desquamation of the paws, scaly tails, inflammation of the eyelids, and bloody discharge from the eyes. Testicular atrophy was observed in all high-dose males at 6, 12, and 24 months. The seminiferous epithelium was atrophied, and the tubular size in the testes was decreased. No treatment-related effects were observed in rats receiving 350 or 117 ppm boron as borax or boric acid. Based on effects observed in the high-dose group, it appears that an MTD was achieved in this study. The study was designed to assess systemic toxicity; only tissues from the brain, pituitary, thyroid, lung, heart, liver, spleen, kidney, adrenal, pancreas, small and large intestine, urinary bladder, testes, ovary, bone, and bone marrow were examined histopathologically, and tumors were not mentioned in

the report. Nevertheless, NTP (1987) concluded that this study provided adequate data on the lack of carcinogenic effects of boric acid in rats and, accordingly, conducted its carcinogenicity study only in mice.

Male and female (50/sex/group) B6C3F1 mice were fed a diet containing 0, 2500, or 5000 ppm boric acid for 103 weeks (NTP, 1987; Dieter, 1994). The low- and high-dose diets provided approximate doses of 275 and 550 mg/kg-day (48 and 96 mg B/kg-day). Mean body weights of high-dose mice were 10-17% lower than those of controls after 32 (males) or 52 (females) weeks. No treatment-related clinical signs were observed throughout the study. Survival of the male mice was significantly lower than that of controls after week 63 in the low-dose group and after week 84 in the high-dose group. Survival was not affected in females. At termination, the survival rates were 82, 60, and 44% in the control, low-, and high-dose males, respectively, and 66, 66, and 74% in the control, low-, and high-dose females, respectively. The low number of surviving males may have reduced the sensitivity of the study for evaluation of carcinogenicity (NTP, 1987).

There was an increased incidence of hepatocellular carcinoma (5/50, 12/50, 8/49) and combined adenoma or carcinoma in low-dose male mice (14/50, 19/50, 15/49) (NTP, 1987; Dieter, 1994). The increase was statistically significant by life table tests, but not by incidental tumor tests. The incidental tumor tests were probably the more appropriate form of statistical analysis in this case because the hepatocellular carcinomas did not appear to be the cause of death for males in this study; the incidence of these tumor types in animals that died prior to study completion (7/30 or 23%) was similar to the incidence at terminal sacrifice (5/20 or 25%) (NTP, 1987; Elwell, 1993). The hepatocellular carcinoma incidence in this study was within the range of male mice historical controls both at the study lab (131/697 or 19% ± 6%) and for NTP (424/2084 or 20% ± 7%) (NTP, 1987; Elwell, 1993). Also, the hepatocellular carcinoma incidence in the male control group of this study (10%) was lower than the historical controls. NTP concluded that the increase in hepatocellular tumors in low dose male mice in this study was not due to administration of boric acid.

There was also a significant increase in the incidence of combined subcutaneous tissue fibromas, sarcomas, fibrosarcomas, and neurofibrosarcomas in low-dose male mice (2/50, 10/50, 2/50) by both incidental and life table pair-wise tests (NTP, 1987; Dieter, 1994). This higher incidence of subcutaneous tissue tumors is within the historical range (as high as 15/50 or 30%) for these tumors in control groups of group-housed male mice from other dosed feed studies (Elwell, 1993). The historical incidence at the study laboratory was 39/697 (6% ± 4%) and in NTP studies was 156/2091 (7% ± 8%) (NTP, 1987). Based on the comparison to historical controls and lack of any increase in the high dose group, NTP concluded that the increase in subcutaneous tumors in low-dose male mice was not compound-related. Overall, NTP concluded that this study produced no evidence of carcinogenicity of boric acid in male

or female mice, although the low number of surviving males may have reduced the sensitivity of the study.

Schroeder and Mitchener (1975) conducted a study in which 0 or 5 ppm of boron as sodium metaborate was administered in the drinking water to groups of 54 male and 54 female Charles River Swiss mice (approximately 0.95 mg B/kg-day) for their life span; controls received deionized water. In adult animals, there generally were no effects observed on body weights (at 30 days, treated animals were lighter than controls, and at 90 days, treated males were significantly heavier than controls) or longevity. The life spans of the dosed group did not differ from controls. Gross and histopathologic examinations were performed to detect tumors. Limited tumor incidence data were reported for other metals tested in this study, but not for boron. Investigators reported that at this dose, boron was not tumorigenic for mice; however, only one dose of boron (lower than other studies) was tested, and an MTD was not reached.

II.A.4. Supporting Data for Carcinogenicity

Results of most short-term studies indicate that boron is not genotoxic. In the streptomycin-dependent *Escherichia coli* Sd-4 assay, boric acid was either not mutagenic (Iyer and Szybalski, 1958; Szybalski, 1958) or produced equivocal results (Demerec et al., 1951). In *Salmonella typhimurium* strains TA1535, TA1537, TA98, and TA100, boric acid was not mutagenic in the presence or absence of rat or hamster liver S-9 activating system (Benson et al., 1984; Haworth et al., 1983; NTP, 1987). Boric acid (concentration, stability, and purity not tested by investigators) was also negative in the Salmonella microsome assay using strains TA1535, TA1537, TA1538, TA98, and TA100 in the presence and absence of rat liver metabolic activation (Stewart, 1991). Although a positive result was reported both with and without metabolic activation for induction of ß-galactosidase synthesis (a response to DNA lesions) in *E. coli* PQ37 (SOS chromotest) (Odunola, 1997), this was an isolated finding.

Results in mammalian systems were all negative. Boric acid (concentration, stability, and purity not tested by investigators) was negative in inducing unscheduled DNA synthesis in primary cultures of male F344 rat hepatocytes (Bakke, 1991). Boric acid did not induce forward mutations in L5178Y mouse lymphoma cells with or without S-9 (NTP, 1987). Boric acid did not induce mutations at the thymidine kinase locus in the L5178Y mouse lymphoma cells in the presence or absence of rat liver activation system (Rudd, 1991). Crude borax ore and refined borax were both negative in assays for mutagenicity in V79 Chinese hamster cells, C3H/1OT1/2 mouse embryo fibroblasts and diploid human foreskin fibroblasts (Landolph, 1985). Similarly, boric acid did not induce chromosome aberrations or increase the frequency of sister chromatid exchanges in Chinese hamster ovary cells with or without rat liver metabolic activating systems (NTP, 1987).

O'Loughlin (1991) performed a micronucleus assay on Swiss-Webster mice (10 animals/sex/dose). Boric acid was administered in deionized water orally (no verification of stability, concentration, or homogeneity was made of the boric acid by the investigators) for 2 consecutive days at 900, 1800, or 3500 mg/kg. Five mice/sex/dose were sacrificed 24 hours after the final dose, and 5/sex/dose were sacrificed 48 hours after the final dose. A deionized water vehicle control (10/sex) and a urethane positive control (10 males) were also tested. Boric acid did not induce chromosomal or mitotic spindle abnormalities in bone marrow erythrocytes in the micronucleus assay in Swiss-Webster mice.

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

Not Applicable

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

Not Applicable

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Documents — U.S. EPA (2004)

This assessment was peer reviewed by a group of external scientists. Comments from the peer reviewers were evaluated carefully and considered by the Agency during the finalization of this assessment. A record of these comments is included in Appendix A of the Toxicological Review of Boron and Compounds (U.S. EPA, 2004). ***To review this appendix, exit to the toxicological review, Appendix A, External Peer Review -- Summary of Comments and Disposition (PDF)***.

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Completion Date — 05/26/2004

II.D.3. EPA Contacts (Carcinogenicity Assessment

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (fax), or hotline.iris@epa.gov (email address).

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — Boron and Compounds
CASRN — 7440-42-8

VI.A. Oral RfD References

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VII. Revision History

Substance Name — Boron and Compounds
CASRN — 7440-42-8
File First On-Line — 10/01/1989

Date	Section	Description
10/01/1989	I.A.	Oral RfD summary on-line
08/05/2004	I.A., I.B., II	Revised RfD, added RfC discussion and added carcinogenicity assessments.

VIII. Synonyms

Substance Name — Boron and Compounds
CASRN — 7440-42-8
Last Revised — 08/05/2004

- 7440-42-8
- BORON