Boron and Compounds
CASRN 7440-42-8
00/00/00

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Boron and Compounds; CASRN 7440-42-8; 00/00/00

Health assessment information on a chemical substance is included in IRIS only after a comprehensive review of chronic toxicity data by U.S. EPA health scientists from several Program Offices, Regional Offices, and the Office of Research and Development. The summaries presented in Sections I and II represent a consensus reached in the review process. Background information and explanations of the methods used to derive the values given in IRIS are provided in the Background Documents.

STATUS OF DATA FOR Boron and Compounds

File First On-Line 10/01/89

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	00/00/00
Inhalation RfC Assessment (I.B.)	on-line	00/00/00
Carcinogenicity Assessment (II.)	on-line	00/00/00

_I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

_I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Boron and Compounds
CASRN -- 7440-42-8
Last Revised -- 00/00/00

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the 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. Please refer to the Background Document for an

elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this 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.

Chronic toxicity in dogs (Weir and Fisher, 1972) was used previously to develop an RfD for boron (10/01/89). 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.I), 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	MF	RfD
Decreased fetal weight (developmental) Rat dietary gestational exposure to boric acid Price et al., 1996a, 1994, 1990; Heindel et al., 1992	BMDL: 10.3 mg/kg-day BMDL(adj) mg/kg-day = 1.16 NOAEL: 9.6 mg B/kg-day	10	1	1E-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). BMDL(adj) calculated by dividing the BMDL by the toxicokinetic adjustment factor of 8.85.

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

Price, C.J., P.L. Strong, M.C. Marr, C.B. Myers and F.J. Murray. 1996a. Developmental toxicity NOAEL and postnatal recovery in rats fed boric acid during gestation. Fund. Appl. Toxicol. 32: 179-193.

Price, C.J., M.C. Marr and C.B. Myers. 1994. Determination of the No-Observable-Adverse-Effect-Level (NOAEL) for Developmental Toxicity in Sprague-Dawley (CD) Rats Exposed to Boric Acid in Feed on Gestational Days 0 to 20 and Evaluation of Postnatal Recovery through Postnatal Day 21. Final report. (3 volumes, 716 pp). RTI Identification No. 65C-5657-200 - Research Triangle Institute, Center for Life Science.

Heindel, J.J., C.J. Price, E.A. Field et al. 1992. Developmental toxicity of boric acid in mice and rats. Fund. Appl. Toxicol. 18: 266-277.

Price, C.J., E.A. Field, M.C. Marr, C.B. Myers, R.E. Morrissey and B.A. Schwetz. 1990. Developmental Toxicity of Boric Acid (CAS No. 10043-35-3) in Sprague Dawley Rats. NTP Report No. 90-105 (and Report Supplement No. 90-105A). National Toxicology Program U.S. DHHS, PHS, NIH, Research Triangle Park, NC, May 1.

Developmental (decreased fetal weights) effects are considered the critical effect. The basis for calculating the RfD is the BMD05 of 10.3 mg boron/kg-day calculated from the developmental effects reported by Heindel et al. (1992; Price et al., 1990) and Price et al. (1996a, 1994).

Heindel et al. (1992; 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 through 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 day 20 of gestation, 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 gestation days 12 through 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 LOAEL of 0.2% boric acid in the feed (28.5 mg B/kg-day) can be established; the maternal 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 and 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 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 agreed that this was the preferred data set for deriving quantitative estimates.

Several benchmark dose (BMDL) 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 and a continuous power model was used. A BMDL 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 BMDL was defined as the 95% lower bound on the dose corresponding to a 5% decrease in the mean (BMR was 5% decrease). For the continuous power model, F-tests that compared the lack of model fit to an estimate of pure error were employed.

For all endpoints, the results of the two 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 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 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; 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; 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 AND MODIFYING FACTORS (ORAL RfD)

UF =10

The uncertainty factors for animal-to-human variability (UF_A) and within-human variability (UF_H) were each split into toxicokinetic and toxicodynamic components (sub-factors). These sub-factors were assigned a default value of half-an-order of magnitude ($10^{0.5}$, or 3). As boron is not metabolized, does not accumulate in the body, and is eliminated almost entirely in the urine, the toxicokinetics are primarily represented by clearance of boron by the kidney. Also, as the critical effect is developmental in nature, only clearance in pregnant females need be considered. Thus, for boron, the toxicokinetic components of both UF_A and UF_H are reduced to 1.0 by a dose-adjustment factor equal to the appropriate pregnant human:pregnant rat ratio of boron clearance. The toxicokinetic adjustment factor (AF_K), which comprises both the interspecies and intrahuman values for toxicokinetics, has been removed from the denominator, as it is no longer an uncertainty, but a known dose-scaling factor. An AF_K of 8.85 was calculated as the ratio of the 5^{th} percentiles of the boron clearance distributions for pregnant rats and pregnant humans, respectively (see Section 3.4.1 of the Toxicological Profile). The 5^{th} percentile was chosen as most representative of the sensitive individuals for both the rat developmental study and for pregnant women (see Section 5.1.3 of the Toxicological Profile). The BMDL was divided by the AF_K of 8.85 to obtain an adjusted BMDL of 1.16 mg/kg-day. The UF of 10 is the product of the default values for the remaining toxicodynamic sub-factors.

MF = 1.

___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 preformed 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 (10/01/89). 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 the small number of test animals per dose group (n=4), 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, the observation of testicular damage in three of four control animals, and 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 that have been reported include 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 affect 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 these 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. 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 U.S. 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.

___I.A.5. CONFIDENCE IN THE ORAL RfD

Study -- High
Data Base -- 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 several subchronic and chronic studies, as well as adequate reproductive and developmental toxicology data. High confidence in the RfD follows.

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

Source Document -- U.S. EPA, 1998

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS summary. A record of these comments is included as an appendix to U.S. EPA, 1998.

Other EPA Documentation -- None

Agency Consensus Date -- __/__/__

___I.A.7. EPA CONTACTS (ORAL RfD)

Please contact the Risk Information Hotline for all questions concerning this assessment or IRIS, in general, at (513)569-7254 (phone), (513)569-7159 (FAX), or RIH.IRIS@EPAMAIL.EPA.GOV (internet address).

__I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Boron and Compounds
CASRN -- 7440-42-8
Last Revised -- 00/00/00

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is generally expressed in units of mg/cu.m. In general, the 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. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F August 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this 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.

NOT VERIFIABLE status indicates that the available data do not meet the minimum data base requirements according to the current Agency methods document for RfDs (EPA/600/8-90/066F October 1994). This does not preclude the use of information in cited references for assessment by others.

___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 in a small 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). This

is consistent with the testicular effects reported in oral studies, but has not been confirmed by other inhalation studies. 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 ($\approx$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 the animals were covered 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 compounds.

___I.B.2. PRINCIPAL AND SUPPORTING STUDIES (INHALATION RfC)

Tarasenko et al. (1972) reported low sperm count, reduced sperm motility and elevated fructose content of seminal fluid in a group of 28 male Russian workers exposed for 10 or more years to high levels of boron aerosols (22-80 mg/m^3) during the production of boric acid. In response to this report and reports of reproductive effects in animal studies (see Section 4.3.2), a controlled epidemiology study of reproductive effects was initiated in U.S. workers exposed to sodium borates.

Whorton et al. (1994a,b, 1992) examined the reproductive effects of sodium borates on male employees at a borax mining and production facility in the United States. A total of 542 subjects participated in the study (72% of the 753 eligible male employees) by answering a questionnaire prepared by the investigators. The median exposure concentration was approximately 2.23 mg/m^3 sodium borate (roughly 0.31 mg B/m^3). Average duration of employment in participants was 15.8 years. Reproductive function was assessed in two ways. First, the number of live births to the wives of workers during the period from 9 months after occupational exposure began through 9 months after it ended was determined, and this number was compared to a number obtained from the national fertility tables for U.S. women (an unexposed control population). Wives of workers and controls were matched for maternal age, parity, race and calendar year. This comparison produced the standardized birth ratio (SBR), defined as the observed number of births divided by the expected number. Secondly, the investigators examined possible deviations of the ratio of male to female offspring relative to the U.S. ratio.

There was a significant excess in the SBR among participants as a whole (Whorton et al., 1994a,b; 1992). Study participants fathered 529 births versus 466.6 expected (SBR=113, $p<0.01$). This excess occurred even though the percentage of participants who had had vasectomies (36%) was 5 times higher than the national average of 7% implicit in the expected number of births. Participants were divided into 5 equal size groups (n = 108/109) based on

average workday exposure to sodium borates (<0.82, 0.82-1.77, 1.78-2.97, 2.98-5.04 and >5.05 mg/m^3). There was no trend in SBR with exposure concentration; the SBR was significantly elevated for both the low and high dose groups, and close to expected for the middle 3 dose groups. There were 42 participants who worked high-exposure jobs for two or more consecutive years. Mean sodium borate exposure in this group was 23.2 mg/m^3 (17.6 - 44.8 mg/m^3) and mean duration of employment in a high-exposure job was 4.9 years (range: 2.1 - 20.4 years). The SBR for these 42 workers was close to expected (102) despite a 48% vasectomy rate. These workers also had elevated SBRs during the actual period of high exposure. An examination of SBR for all participants by 5-year increments from 1950 to 1990 revealed no significant trend in either direction over time.

Analyses of the percentage of female offspring showed an excess of females that approached statistical significance (52.7% vs. 48.8% in controls) (Whorton et al., 1994a,b; 1992). This excess was not related to exposure, however, as percent female offspring decreased with increasing sodium borate exposure concentration from 55.3% in the low dose group to 49.2% in the high dose group. Moreover, individuals with 2 or more consecutive years in high borate exposure jobs had more boys than girls. The investigators concluded that exposure to inorganic borates did not appear to adversely affect fertility in the population studied. This study, while adequately conducted, has several inherent limitations. Thus, the human data are insufficient to determine if boron may cause male reproductive toxicity (IEHR, 1997).

Whorton et al. (1992) also studied the effects of borates on reproductive function of exposed female employees. Reproductive function was assessed in the same way as it was for wives of male employees. A total of 81 employees were eligible, 68 of whom participated in the study. No information was provided regarding matching of the exposed and control groups. The SBR was 90 (32 offspring observed, 35.4 expected), indicating a deficiency, although not statistically significant, in live births among exposed females. When the data were analyzed per exposure category, the 76 employees (some nonparticipants apparently were included) in the low and medium exposure category showed a nonstatistically significant deficit of births (37) compared to 43.5 expected (SBR=85). No statistical differences were observed between exposed and controls when the results were analyzed by exposure categories. The authors concluded that the exposure to inorganic borates did not appear to affect fertility in the population studied. It must be recognized, however, that the rather small sample size may have precluded a meaningful statistical analysis of the results.

Culver et al. (1994) monitored boron levels in the blood and urine of workers exposed to borate dust (borax, borax pentahydrate and anhydrous borax) at a borax production facility. The workers were divided into three groups according to borate exposure. Workers in both the medium and high exposure categories had significantly increased levels of boron in the blood after working Monday (≈0.25 µg/g) in comparison to pre-shift Monday morning values (≈0.1 µg/g). Similarly, workers in the high exposure category had significantly higher urinary boron levels Monday post-shift (≈12 µg/mg creatinine) than pre-shift (≈2 µg/mg creatinine). Boron in the diets (which were assigned by the researchers to ensure uniformity among workers) and workplace air was also monitored during this study. A higher proportion of total boron intake

was from air than from diet, and both blood and urine boron were best modeled based on air concentration of boron alone (i.e., inclusion of dietary boron as an independent variable did not increase the predictive power of the models). These data show that boron was absorbed during the work day, and that borate dust in the air was the source of the additional boron in the blood and urine. However, it is not clear what amount of the inhaled boron was actually absorbed through the respiratory tract. The researchers speculated that due to the large size of the dust particles in the work area, most of the inhaled borate would have been deposited in the upper respiratory tract, where it could have been absorbed directly through the mucous membranes or could have been cleared by mucociliary activity and swallowed.

Swan et al. (1995) investigated the relationship between spontaneous abortion in women employed in the semiconductor manufacturing industry and various chemical and physical agents used in the industry, including boron. The study population consisted of 904 current and former female employees who became pregnant while working at one of 14 U.S. semiconductor companies between 1986 and 1989. Approximately one-half of those included were fabrication workers with some chemical exposure. Exposure classifications were based on jobs held at conception and level of exposure to specific agents during the first trimester. The risk of spontaneous abortion was increased in fabrication workers compared with other workers, and particularly within the subgroup of workers who performed masking (a group with relatively low boron exposure). No significant association was found between exposure to boron and spontaneous abortion risk.

The respiratory and irritant effects of industrial exposure to boron compounds have also been studied. The studies were conducted at the same borax mining and production facility as the reproduction study of Whorton et al. (1994a,b; 1992). A health survey of workers at the plant found complaints of dermatitis, cough, nasal irritation, nose bleeds and shortness of breath (Birmingham and Key, 1963). Air concentrations of borate dust were not reported, but were high enough to interfere with normal visibility. In response to this report, a cross-sectional study of respiratory effects (questionnaire, spirometric testing, roentgenograms) was performed on 629 male workers at the plant (Ury, 1966). The study was inconclusive, but did find suggestive evidence for an association between respiratory ill health and inhalation exposure to dehydrated sodium borate dust based on analysis of FEV and respiratory illness data in the subgroup of 82 men who had worked for at least one year at the calcining and fusing processes compared with the other 547 who had never worked at these processes.

Additional studies were performed by Garabrant et al. (1984, 1985). Garabrant et al. (1985) studied a group of 629 workers employed for 5 or more years at the plant and employed in an area with heavy borax exposure at the time of the study (93% of those eligible). Workers were categorized into 4 groups according to borax exposure (1.1, 4.0, 8.4 and 14.6 mg/m^3 borax), and frequency of acute and chronic respiratory symptoms was determined. Statistically significant, positive dose-related trends were found for (in order of decreasing frequency) dryness of mouth, nose or throat, eye irritation, dry cough, nose bleeds, sore throat, productive cough, shortness of breath and chest tightness. Frequency of these symptoms in the high dose group ranged from 33% down to 5%. Pulmonary function tests and chest x-rays were not affected by borax

exposure. The researchers concluded that borax appears to cause simple respiratory irritation that leads to chronic bronchitis with no impairment of respiratory function at the exposure levels in this study. Irritation occurred primarily at concentrations of 4.4 mg/m^3 or more. Garabrant et al. (1984) studied a subgroup of the 629 workers who were exposed to boric oxide and boric acid. Workers who had held at least one job in an area with boron oxide or boric acid exposure (n=113) were compared with workers who had never held a job in an area with boron oxide or boric acid but had held at least one job in an area with low or minimal exposure to borax (n=214). The boron oxide/boric acid workers had significantly higher rates of eye irritation, dryness of mouth, nose or throat, sore throat and productive cough. Mean exposure was 4.1 mg/m^3, with a range of 1.2 to 8.5 mg/m^3. The researchers concluded that boron oxide and boric acid produce upper respiratory and eye irritation at less than 10 mg/m^3.

Wegman et al. (1994) conducted a longitudinal study of respiratory function in workers with chronic exposure to sodium borate dusts. Participants in the Garabrant et al. (1985) study were re-tested for pulmonary function 7 years after the original survey. Of the 629 participants in the original study in 1981, 371 were available for re-testing in 1988. Of these, 336 performed pulmonary function tests (303 produced acceptable tests in both years). Cumulative exposure was estimated for each participant for the years 1981-1988 as a time-weighted sum of the exposure in each job held during that time. Exposure prior to 1981 was not included due to the scarcity of monitoring data for those years. Pulmonary function (FEV_1, FVC) in study subjects declined over the 7-year period at a rate very close to that expected based on standard population studies. Cumulative borate exposure over the years 1981-1988 was not related to the change in pulmonary function. Acute studies showed statistically significant, positive dose-related increases in eye, nasal and throat irritation, cough and breathlessness with borate exposure (6-hr TWA or 15-min TWA). The same relationships were present when effects were limited to moderate severity or higher. There was no evidence for an effect of borate type (decahydrate, pentahydrate, anhydrous) on response rate.

There are few data available regarding the toxicity of boron compounds by inhalation in laboratory animals. Wilding et al. (1959) investigated the toxicity of boron oxide aerosols by inhalation exposure in rats and dogs. A group of 70 albino rats, including both males and females, was exposed to an average concentration of 77 mg/m^3 of boron oxide aerosols (24 mg B/m^3) for 24 weeks (6 hours/day, 5 days/week). Additional groups of rats were exposed to 175 mg/m^3 (54 mg B/m^3) for 12 weeks (n=4) or 470 mg/m^3 (146 mg B/m^3) for 10 weeks (n=20) using the same exposure regimen. At the latter concentration, the aerosol formed a dense cloud of fine particles, and the animals were covered with dust. Also in this study, 3 dogs were exposed to 57 mg/m^3 (18 mg B/m^3) for 23 weeks. No clinical signs were noted, except a slight reddish exudate from the nose of rats exposed to 470 mg/m^3, which the researchers attributed to local irritation. Growth was reduced roughly 9% in rats exposed to 470 mg/m^3 compared to controls. Growth in the lower dose groups and in dogs was not affected. There was a significant drop in pH, and increase in urine volume, in rats exposed to 77 mg/m^3. The researchers hypothesized that this was due to formation of boric acid from boron oxide by hydration in the body and the diuretic properties of boron oxide. There was also a significant increase in urinary creatinine at this dose. No effect on serum chemistry, hematology, organ weights, histopathology (including the testis), bone strength

or liver function was found in either rats or dogs (not all endpoints were studied in all exposure groups).

___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, 1998

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS summary. A record of these comments is included as an appendix to U.S. EPA, 1998.

Other EPA Documentation -- None

Agency Consensus Date -- __/__/__

___I.B.7. EPA CONTACTS (INHALATION RfC)

Please contact the Risk Information Hotline for all questions concerning this assessment or IRIS, in general, at (513)569-7254 (phone), (513)569-7159 (FAX), or RIH.IRIS@EPAMAIL.EPA.GOV (internet address).

_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Boron and Compounds
CASRN -- 7440-42-8
Last Revised -- 00/00/00

Section II 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 exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per µg/L drinking water or risk per µg/cu.m air breathed. The third form in which risk is presented is a concentration of the chemical in drinking water or air associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

__II.A. EVIDENCE FOR HUMAN CARCINOGENICITY

___II.A.1. WEIGHT-OF-EVIDENCE CHARACTERIZATION

Classification -- Under EPA's current guidelines for carcinogen risk assessment (U.S. EPA, 1986), boron is classified as Group D; not classifiable as to human carcinogenicity. Under the new proposed guidelines (U.S. EPA, 1996), the data are considered to be inadequate for evaluation of the human carcinogenic potential of boron.

Basis -- 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*.

___II.A.2. HUMAN CARCINOGENICITY DATA

No studies were located regarding the carcinogenicity of boron in humans.

___II.A.3. ANIMAL CARCINOGENICITY DATA

Weir and Fisher (1972) fed Sprague-Dawley rats a diet containing 0, 117, 350 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 β-galactosidase synthesis (a response to DNA lesions) in *E. coli* PQ37 (SOS chromotest) (Odunola, 1997), this is an isolated finding at present.

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 Document -- U.S. EPA, 1998

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS summary. A record of these comments is included as an appendix to U.S. EPA, 1998.

___II.D.2. EPA REVIEW (CARCINOGENICITY ASSESSMENT)

Agency Consensus Date -- __/__/__

___II.D.3. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Please contact the Risk Information Hotline for all questions concerning this assessment or IRIS, in general, at (513)569-7254 (phone), (513)569-7159 (FAX), or RIH.IRIS@EPAMAIL.EPA.GOV (internet address).

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___VI. BIBLIOGRAPHY

Boron and Compounds
CASRN -- 7440-42-8
Last Revised -- 00/00/00

___VI.A. ORAL RfD REFERENCES

Allen, B.C., P.L. Strong, C.J. Price, S.A. Hubbard and G.P. Datson. 1996. Benchmark dose analysis of the developmental toxicity in rats exposed to boric acid. Fund. Appl. Toxicol. 32: 194-204.

Anderson, D.L., W.C. Cunningham and T.R. Lindstrom. 1994. Concentrations and intakes of H, B, S, K, Na, Cl, and NaCl in foods. J. Food Comp. Anal. 7: 59-82.

Clarke, W.B. and R.S. Gibson. 1988. Lithium, boron and nitrogen in 1-day diet composites and a mixed-diet standard. J. Food Comp. Anal. 1: 209-220.

Cox, D. and D. Lindley. 1974. Theoretical Statistics. Chapman & Hall, London.

Dixon, R.L., R.J. Sherins and I.P. Lee. 1979. Assessment of environmental factors affecting male fertility. Environ. Health Perspect. 30: 53-68.

ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals). 1994. Reproductive and General Toxicology of some Inorganic Borates and Risk Assessment for Human Beings. Technical Report No. 65. Brussels, December.

Fail, P.A., J.D. George, J.C. Seely, T.B. Grizzle and J.J. Heindel. 1991. Reproductive toxicity of boric acid in Swiss (CD-1) mice: Assessment using the continuous breeding protocol. Fund. Appl. Toxicol. 17: 225-239.

Field, E.A., C.J. Price, M.C. Marr, C.B. Myers and R.E. Morrissey. 1989. Developmental Toxicity of Boric Acid (CAS No. 10043-35-3) in CD-1-Swiss Mice. NTP Final Report No. 89-250. National Toxicology Program, U.S. DHHS, PHS, NIH, Research Triangle Park, NC, August 11.

Heindel, J.J., C.J. Price, E.A. Field et al. 1992. Developmental toxicity of boric acid in mice and rats. Fund. Appl. Toxicol. 18: 266-277.

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

Hunt, C.D. 1994. The biochemical effects of physiologic amounts of dietary boron in animal nutrition models. Environ. Health Perspect. 102(Suppl 7): 35-43.

IEHR (Institute for Evaluating Health Risks). 1997. An assessment of boric acid and borax using the IEHR evaluative process for assessing human developmental and reproductive toxicity of agents. Reproductive Toxicology 11: 123-160.

Iyengar, G.V., W.B. Clarke, R.G. Downing and J.T. Tanner. 1988. Lithium in biological and dietary materials. Proc. Intl. Workshop, Trace Elem. Anal. Chem. Med. Biol. 5: 267-269.

Kavlock, R.J., B.C. Allen, E.M. Faustman and C.A. Kimmel. 1995. Dose-response assessments for developmental toxicity: IV. Benchmark doses for fetal weight changes. Fund. Appl. Toxicol. 26: 211-222.

Ku, W.W., R.E. Chapin, R.N. Wine and B.C. Gladen. 1993. Testicular atrophy of boric acid (BA): Relationship of dose to lesion development and recovery in F344 rat. Reprod. Toxicol. 7: 305-319.

Linder, R.E., L.F. Strader and G.L. Rehnberg. 1990. Effect of acute exposure to boric acid on the male reproductive system of the rat. J. Toxicol. Environ. Health. 31: 133-146.

Mertz, W. 1993. Essential trace metals: new definitions based on new paradigms. Nutr. Rev. 51: 287-295.

Nielsen, F.H. 1991. Nutritional requirements for boron, silicon, vanadium, nickel, and arsenic: Current knowledge and speculation. FASEB J. 5: 2661-2667.

Nielsen, F.H. 1992. Facts and fallacies about boron. Nutr. Today. 27: 6-12.

Nielsen, F.H. 1994. Biochemical and physiologic consequences of boron deprivation in humans. Environ. Health Perspect. 102(Suppl. 7): 59-63.

Nielsen, F.H., C.D. Hunt, L.M. Mullen and J.R. Hunt. 1987. Effect of dietary boron on minerals, estrogen, and testosterone metabolism in post-menopausal women. FASEB J. 1: 394-397.

NRC (National Research Council). 1989. Recommended Dietary Allowances, 10th ed. National Academy Press, Washington, DC. p. 267.

NTP (National Toxicology Program). 1987. Toxicology and Carcinogenesis Studies of Boric Acid (CAS No. 10043-35-3) in B6C3F1 Mice (feed studies). NTP Tech. Rep. Ser. No. 324. U.S. DHHS, PHS, NIH, Research Triangle Park, NC.

Price, C.J., E.A. Field, M.C. Marr, C.B. Myers, R.E. Morrissey and B.A. Schwetz. 1990. Developmental Toxicity of Boric Acid (CAS No. 10043-35-3) in Sprague Dawley Rats. NTP Report No. 90-105 (and Report Supplement No. 90-105A). National Toxicology Program, U.S. DHHS, PHS, NIH, Research Triangle Park, NC, May 1.

Price, C.J., M.C. Marr, C.B. Myers, J.J. Heindel and B.A. Schwetz. 1991. Developmental Toxicity of Boric Acid (CAS No. 10043-35-3) in New Zealand White Rabbits. NTP TER-90003. National Toxicology Program, U.S. DHHS, PHS, NIH, Research Triangle Park, NC, November (and Laboratory Supplement No. TER-90003, December).

Price, C.J., M.C. Marr and C.B. Myers. 1994. Determination of the No-Observable-Adverse-Effect Level (NOAEL) for Developmental Toxicity in Sprague-Dawley (CD) Rats Exposed to Boric Acid in Feed on Gestational Days 0 to 20, and Evaluation of Postnatal Recovery through Postnatal Day 21. Final report. (3 volumes, 716 pp). RTI Identification No. 65C-5657-200. Research Triangle Institute, Center for Life Science, Research Triangle Park, NC.

Price, C.J., P.L. Strong, M.C. Marr, C.B. Myers and F.J. Murray. 1996a. Developmental toxicity NOAEL and postnatal recovery in rats fed boric acid during gestation. Fund. Appl. Toxicol. 32: 179-193.

Price, C.J., M.C. Marr, C.B. Myers, J.C. Seely, J.J. Heindel and B.A. Schwetz. 1996b. The developmental toxicity of boric acid in rabbits. Fund. Appl. Toxicol. 34: 176-187.

Renwick, A.G. 1991. Safety factors and establishment of acceptable daily intake. Food Add. Contam. 8(2): 135-150.

Seal, B.S. and H.J. Weeth. 1980. Effect of boron in drinking water on the male laboratory rat. Bull. Environ. Contam. Toxicol. 25: 782-789.

TERA (Toxicology Excellence for Risk Assessment). 1997. Toxicokinetics and Toxicodynamics of Boron: Effect on the Derivation of an Uncertainty Factor for Development of a Tolerable Intake. September 30, 1997.

Treinen, K.A. and R.E. Chapin. 1991. Development of testicular lesions in F344 rats after treatment with boric acid. Toxicol. Appl. Pharmacol. 107: 325-335.

U.S. Borax Research Corp. 1963. MRID No. 00068026; HED Doc. No. 009301. Available from EPA. Write to FOI, EPA, Washington, DC. 20460.

U.S. Borax Research Corp. 1966. MRID No. 00005622, 00068021, 00068881; HED Doc. No. 009301. Available from EPA. Write to FOI, EPA, Washington, DC. 20460.

U.S. Borax Research Corp. 1967. MRID No. 00005623, 005624; HED Doc. No. 009301. Available from EPA. Write to FOI, EPA, Washington, DC. 20460.

U.S. EPA. 1980. Guidelines and Methodology Used in the Preparation of Health Effect Assessment Chapters of the Consent Decree Water Criteria Documents. Federal Register. 45(231): 79347-79357.

U.S. EPA. 1988. Recommendations for and documentation of biological values for use in risk assessment. EPA 600/6-87/008, NTIS PB88-179874/AS, February 1988.

U.S. EPA. 1998. Toxicological Review of Boron and Compounds in Support of Summary Information on Integrated Risk Information System (IRIS). National Center for Environmental Assessment, Washington, DC. Available on line from: http://www.epa.gov/iris

Weir, R.J. and R.S. Fisher. 1972. Toxicologic studies on borax and boric acid. Toxicol. Appl. Pharmacol. 23: 351-364.

WHO (World Health Organization). 1998. Environmental Health Criteria 204: Boron. International Programme on Chemical Safety, Geneva, Switzerland. ISBN 92 4 157204 3.

___VI.B. INHALATION RfC REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 1991. Documentation of Threshold Limit Values and Biological Exposure Indices for Chemical Substances in the Workroom Air, 6th ed. ACGIH, Cincinnati, OH.

Birmingham, D.J. and M.M. Key. 1963. Preliminary Survey, U.S. Borax Plant, Boron, CA (February 20, 1963). Occupational Health Research and Training Facility, Division of Occupational Health, Public Health Service, U.S. Dept. Of Health, Education and Welfare, Cincinnati, OH. (Cited in ACGIH, 1991)

Garabrant, D.H., L. Bernstein, J.M. Peters and T.J. Smith. 1984. Respiratory and eye irritation from boron oxide and boric acid dusts. J. Occup. Med. 26: 584-586.

Garabrant, D.H., L. Bernstein, J.M. Peters, et al. 1985. Respiratory effects of borax dust. Br. J. Ind. Med. 42: 831-837.

IEHR (Institute for Evaluating Health Risks). 1997. An assessment of boric acid and borax using the IEHR evaluative process for assessing human developmental and reproductive toxicity of agents. Reprod. Toxicol. 11: 123-160.

Swan, S.H., J.J. Beaumont, S.K. Hammond et al. 1995. Historical cohort study of spontaneous abortion among fabrication workers in the semiconductor health study: agent-level analysis. Am. J. Indust. Med. 28: 751-769.

Tarasenko, N.Y., A.A. Kasparov and O.M. Strongina. 1972. Effect of boric acid on the generative function in males. Gig. Tr. Prof. Zabol. 11: 13-16. (Cited in Whorton et al., 1994b)

Ury, H.K. 1966. Interim Report on the 1963 Respiratory Disease Survey at Boron, CA. Air Pollution Medical Studies Unit, Bureau of Chronic Diseases, California State Dept. of Public Health. (Cited in ACGIH, 1991)

U.S. EPA. 1998. Toxicological Review of Boron and Compounds in Support of Summary Information on Integrated Risk Information System (IRIS). National Center for Environmental Assessment, Washington, DC. Available on line from: http://www.epa.gov/iris

Wegman, D.H., E.A. Eisen, X. Hu et al. 1994. Acute and chronic respiratory effects of sodium borate particulate exposures. Environ. Health Perspect. 102(Suppl 7): 119-128.

Whorton, D., J. Haas and L. Trent. 1992. Reproductive Effects of Inorganic Borates on Male Employees: Birth Rate Assessment Report. Prepared for United States Borax & Chemical Corporation. Document No. 6966001.

Whorton, D., J. Haas and L. Trent. 1994a. Reproductive effects of inorganic borates on male employees: birth rate assessment. Environ. Health Perspect. 102(Suppl 7): 129-131.

Whorton, M.D., J.L. Haas, L. Trent and O. Wong. 1994b. Reproductive effects of sodium borates on male employees: birth rate assessment. Occup. Environ. Med. 51: 761-767.

Wilding, J.L., W.J. Smith, P. Yevich et al. 1959. The toxicity of boron oxide. Am. Ind. Hyg. Assoc. J. 20: 284-289.

___VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

Bakke, J.P. 1991. Evaluation of the potential of boric acid to induce unscheduled DNA synthesis in the in vitro hepatocyte DNA repair assay using the male F-344 rat. (Unpublished study) Submitted by U.S. Borax Corp. MRID No. 42038903.

Benson, W.H., W.J. Birge and H.W. Dorough. 1984. Absence of mutagenic activity of sodium borate (borax) and boric acid in the Salmonella preincubation test. Environ. Toxicol. Chem. 3: 209-214.

Demerec, M., G. Bentani and J. Flint. 1951. A survey of chemicals for mutagenic action on E. coli. Am. Nat. 84: 119-136.

Dieter, M.P. 1994. Toxicity and carcinogenicity studies of boric acid in male and female $B6C3F_1$ mice. Environ. Health Perspect. 102(Suppl 7): 93-97.

Elwell, M. 1993. Letter to C. Smallwood, U.S. EPA, Cincinnati, OH. March 5.

Haworth, S., T. Lawlor, K. Mortelmans, W. Speck and E. Zeiger. 1983. Salmonella mutagenicity test results for 250 chemicals. Environ. Mutagen. (Suppl.) 1: 3-142.

Iyer, V.N. and W. Szybalski. 1958. Two simple methods for the detection of chemical mutagens. Appl. Microbiol. 6: 23-29.

Landolph, J.R. 1985. Cytotoxicity and negligible genotoxicity of borax ores to cultured mammalian cells. Am. J. Ind. Med. 7: 31-43.

NTP (National Toxicology Program). 1987. Toxicology and carcinogenesis studies of boric acid (CAS No. 10043-35-3) in B6C3F1 mice (feed studies). NTP Tech. Rep. Ser. No. 324. U.S. DHHS, PHS, NIH, Research Triangle Park, NC.

Odunola, O.A. 1997. Individual and combined genotoxic response of boric acid and aflotoxin B_1 in *Escherichia coli* PQ37. East Afr. Med. J. 74: 499-502.

O'Loughlin, K.G. 1991. Bone marrow erythrocyte micronucleus assay of boric acid in Swiss-Webster mice. (Unpublished study) Submitted by U.S. Borax Corp. MRID No. 42038904.

Rudd, C.J. 1991. Mouse lymphoma cell mutagenesis assay (tK+/-/tK-/-) of boric acid. (Unpublished study) Submitted by U.S. Borax Corp. MRID No. 4203902.

Schroeder, H.A. and M. Mitchener. 1975. Life-term effects of mercury, methyl mercury, and nine other trace metals on mice. J. Nutr. 105: 453-458.

Stewart, K.R. 1991. Salmonella/microsome plate incorporation assay of boric acid. (Unpublished study) Submitted by U.S. Borax Corp. MRID No. 4203901.

Szybalski, W. 1958. Special microbiological system. II. Observations of chemical mutagenesis in microorganisms. Ann. NY Acad. Sci. 76: 475-489.

U.S. EPA. 1986. Guidelines for carcinogen risk assessment. Federal Register 51(185): 33992-34003.

U.S. EPA. 1996. Proposed guidelines for carcinogen risk assessment. Federal Register 61(79): 17960-18011.

U.S. EPA. 1998. Toxicological Review of Boron and Compounds in Support of Summary Information on Integrated Risk Information System (IRIS). National Center for Environmental Assessment, Washington, DC. Available on line from: http://www.epa.gov/iris

Weir, R.J. and R.S. Fisher. 1972. Toxicologic studies on borax and boric acid. Toxicol. Appl. Pharmacol. 23: 351-364.

___VII. REVISION HISTORY

Boron and Compounds
CASRN -- 7440-42-8

Date	Section	Description
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___VIII. SYNONYMS

Boron and Compounds
CASRN -- 7440-42-8
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